# THE American Journal OF Gastroenterology

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## A Journal of Clinical Gastroenterology

**VOL. 71, NO. 1** **JANUARY, 1979**

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***21, 22, 23, 24 October 1979***

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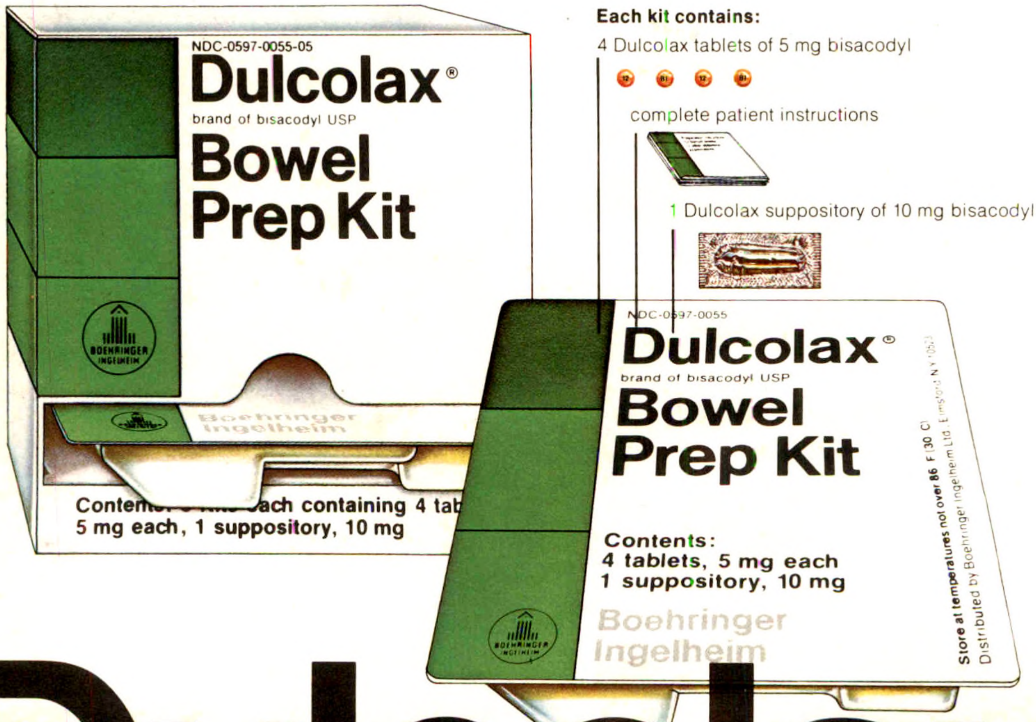
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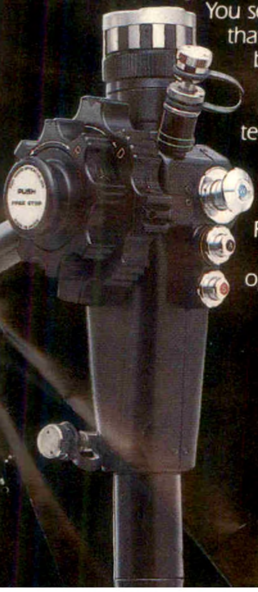

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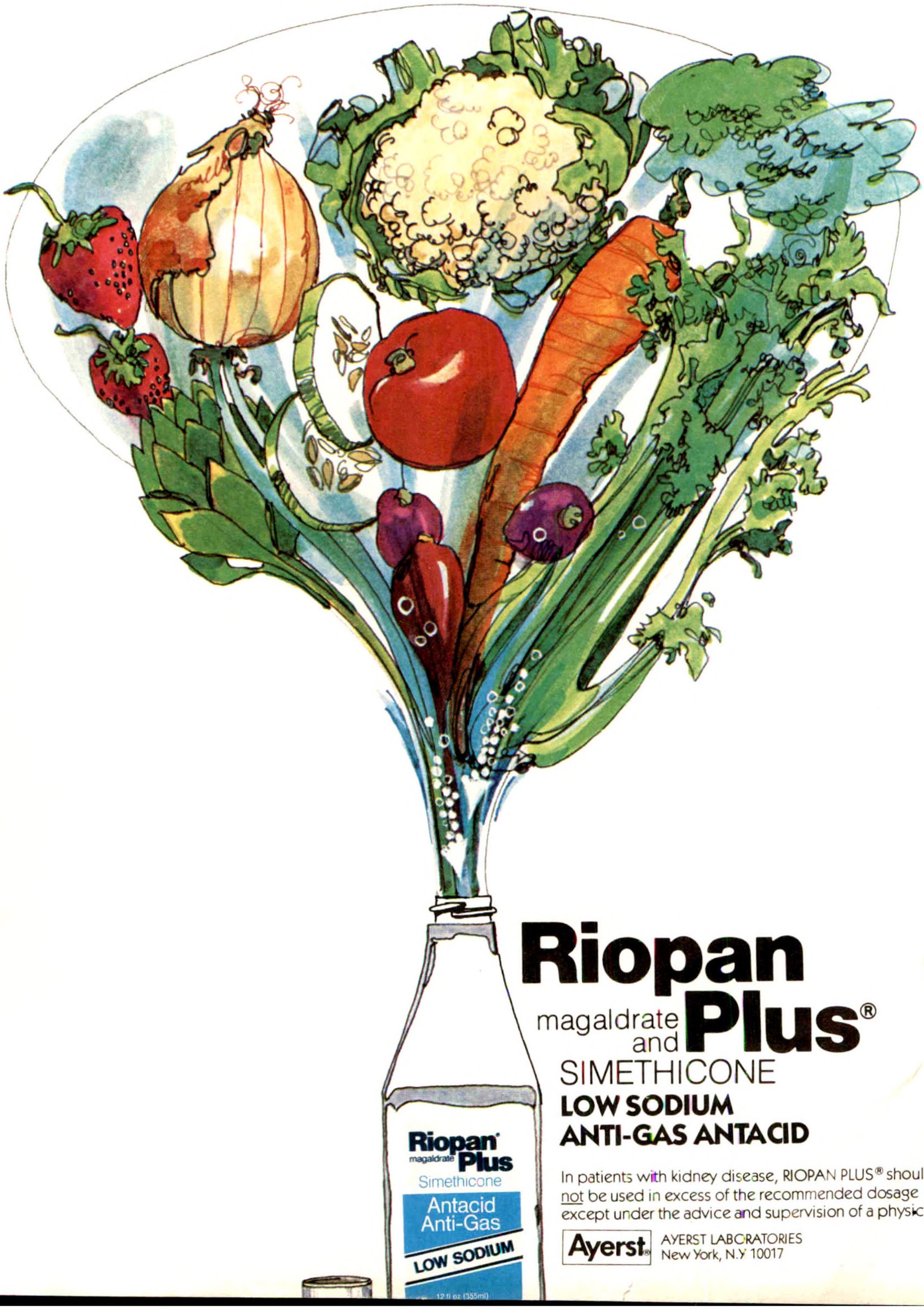

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VOL. 71, NO. 1 JANUARY, 1979

# THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

*The Pioneer Journal of Clinical Gastroenterology, Proctology and Allied Subjects in the United States and Canada*

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gastroenterology or allied subjects. It may be impossible to review all material sent. However, an a
will be made in the Department of Reviews.

**Correspondence:** We welcome Letters to the Editor, which if suitable, and space permits, will be publish
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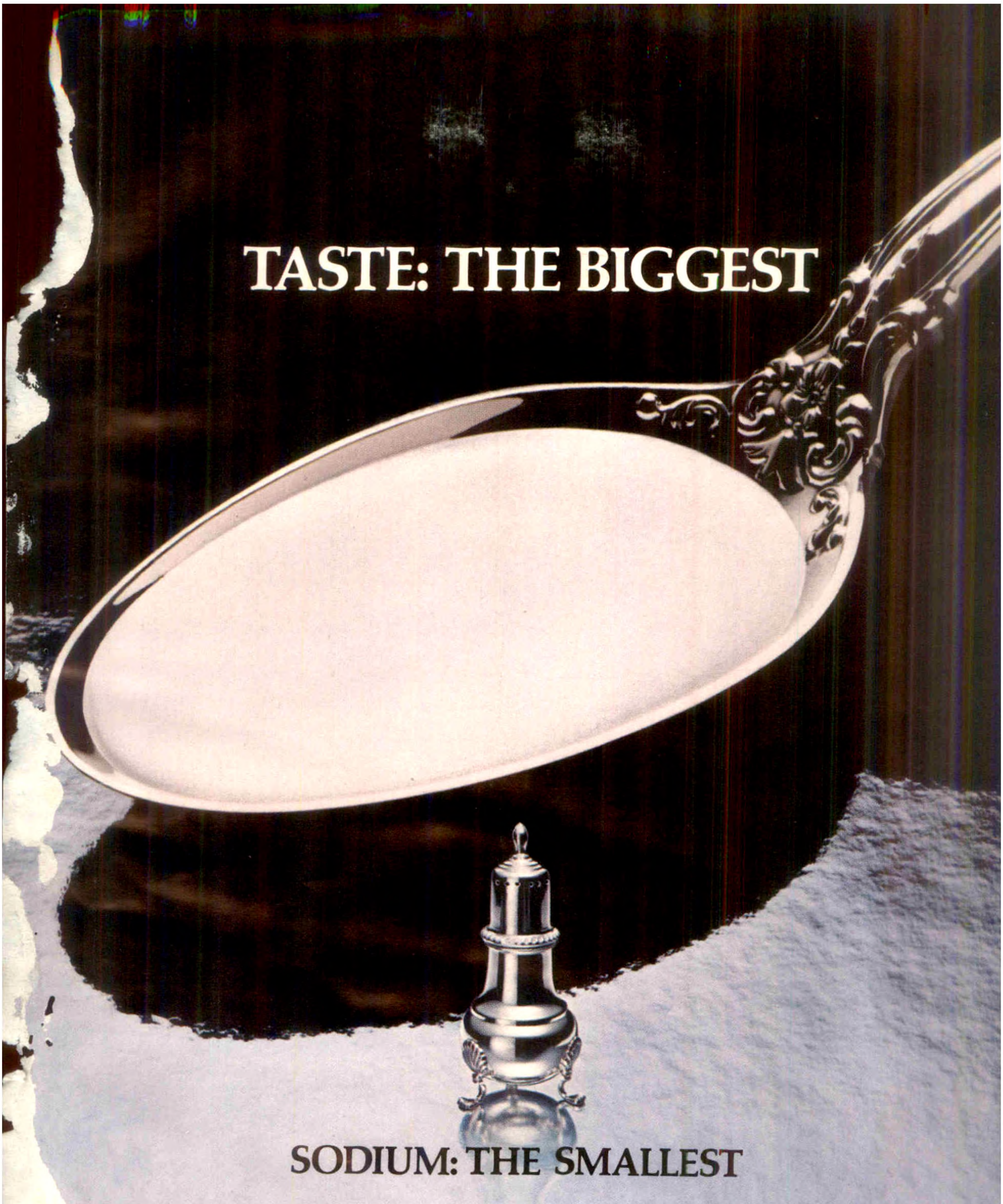

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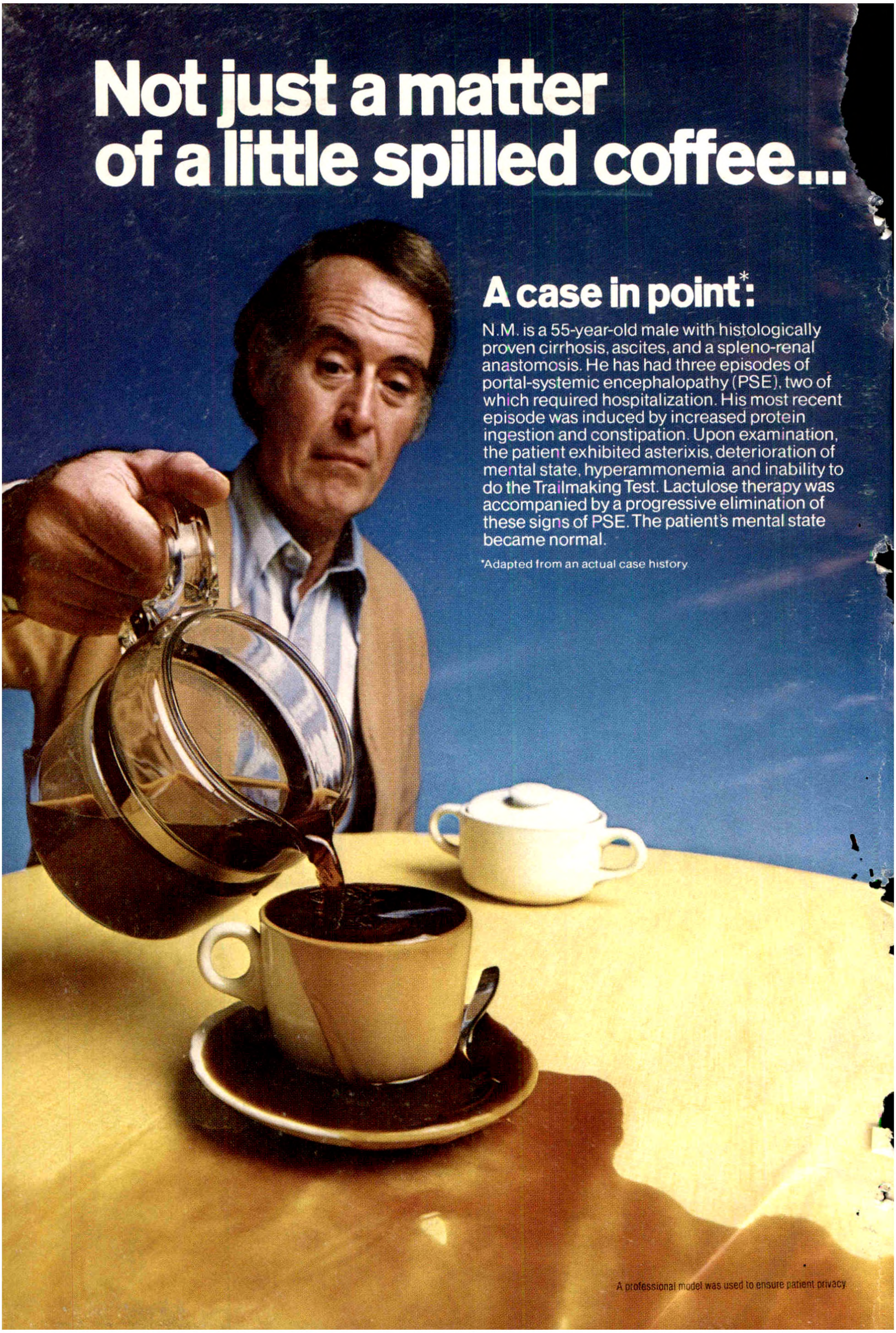

# Not just a matter of a little spilled coffee...

## A case in point*:

N.M. is a 55-year-old male with histologically proven cirrhosis, ascites, and a spleno-renal anastomosis. He has had three episodes of portal-systemic encephalopathy (PSE), two of which required hospitalization. His most recent episode was induced by increased protein ingestion and constipation. Upon examination, the patient exhibited asterixis, deterioration of mental state, hyperammonemia and inability to do the Trailmaking Test. Lactulose therapy was accompanied by a progressive elimination of these signs of PSE. The patient's mental state became normal.

*Adapted from an actual case history.

A professional model was used to ensure patient privacy.

# ...this is portal-systemic encephalopathy (PSE)–

*(Also called Hepatic Encephalopathy, pre-Hepatic Coma)*

# –a common complication of chronic liver disease.

## Suspect PSE in every patient with cirrhosis.

### Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

### Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

### Treat PSE with Cephulac (lactulose) Syrup

- relieves PSE in 75% of episodes
- acts without serious adverse reactions
- lowers blood ammonia levels
- improves EEG and mental state
- permits more normal dietary protein intake
- provides an easy-to-manage means of long-term therapy

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# (lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

## for the prevention and treatment of PSE in your patients with chronic liver disease

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**Brief Summary**

**INDICATIONS:** For the prevention and treatment of portal-systemic
encephalopathy, including the stages of hepatic pre-coma and coma. Co
trolled studies have shown that lactulose syrup therapy reduces the blood
ammonia levels by 25-50%; this is generally paralleled by an improvemen
the patients' mental state and by an improvement in EEG patterns. The cli
cal response has been observed in about 75% of patients, which is at leas
as satisfactory as that resulting from neomycin therapy. An increase in
patients' protein tolerance is also frequently observed with lactulose thera
In the treatment of chronic portal-systemic encephalopathy, Cephulac ha
been given for over 2 years in controlled studies.

**CONTRAINDICATIONS:** Since Cephulac contains galactose (less than
2.2 g./15 ml.), it is contraindicated in patients who require a low galactos

**WARNINGS:** *Use in Pregnancy:* Studies in laboratory animals have not
revealed a teratogenic potential of lactulose. The safety of lactulose syrup
during pregnancy and its effect on the mother or the fetus have not been
evaluated in humans. The physician and patient should understand that t
possibility that lactulose syrup might cause damage to the human fetus c
not be excluded. Lactulose syrup should not be given during pregnancy
unless, in the opinion of the physician, the possible benefits outweigh the
possible risks.

**PRECAUTIONS:** Lactulose syrup contains galactose (less than 2.2 g./1
ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with cauti
in diabetics. There have been conflicting reports about the concomitant u
of neomycin and lactulose syrup. Theoretically, the elimination of certain
colonic bacteria by neomycin and possibly other anti-infective agents ma
interfere with the desired degradation of lactulose and thus prevent the a
fication of colonic contents. Thus the status of the lactulose-treated patie
should be closely monitored in the event of concomitant oral anti-infectiv
therapy. Other laxatives should not be used especially during the initial p
of therapy for portal-systemic encephalopathy because the loose stools
resulting from their use may falsely suggest that adequate Cephulac dos
has been achieved. In the overall management of portal-systemic enceph
lopathy it should be recognized that there is serious underlying liver dise
with complications such as electrolyte disturbance (e.g., hypokalemia) fo
which other specific therapy may be required.

**ADVERSE REACTIONS:** Cephulac may produce gaseous distention wi
flatulence or belching and abdominal discomfort such as cramping in ab
20% of patients. Excessive dosage can lead to diarrhea. Nausea and vo
ing have been reported infrequently.

**DOSAGE AND ADMINISTRATION:** The usual dosage is 2 to 3 tablesp
fuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four tim
daily. The dosage may be adjusted every day or two to produce 2 or 3 so
stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to ind
the rapid laxation indicated in the initial phase of the therapy of portal-
systemic encephalopathy. When the laxative effect has been achieved, th
dose of Cephulac may then be reduced to the recommended daily dose.
Improvement in the patient's condition may occur within 24 hours but ma
not begin before 48 hours or even later. Continuous long-term therapy is
indicated to lessen the severity and prevent the recurrence of portal-
systemic encephalopathy. The dose of Cephulac for this purpose is the s
as the recommended daily dose.

Product Information as of August, 1975

**References:**
1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalop
Digestion 14 548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non
cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hep
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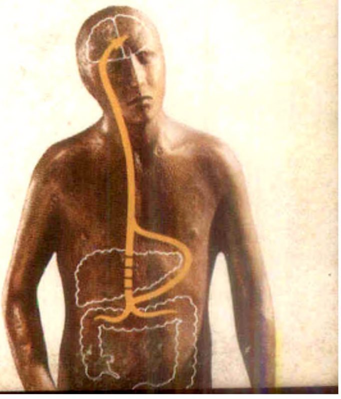

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These, in addition to other original articles, selected abstracts, editorials, book reviews, Radiology Corners, Endoscopy Corners, Pediatric Corners and "State of the Art" review articles.

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**INDICATIONS:** Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
**CONTRAINDICATIONS:** Systemic fungal infections; recent ileocolostomy.
**WARNINGS:** In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

*Usage in pregnancy:* Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

*Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response.* Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
**PRECAUTIONS:** Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
**ADVERSE REACTIONS:** Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:

*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis, vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism
**DOSAGE AND ADMINISTRATION:** CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
**HOW SUPPLIED:** Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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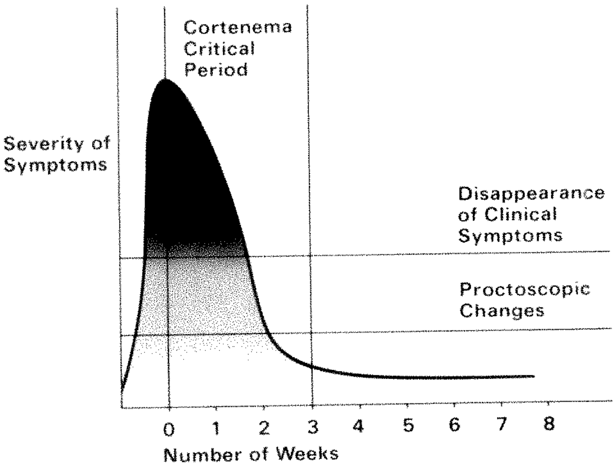

Once a diagnosis is established, Cortenema often is the only medication required for treatment of mild to moderate distal ulcerative colitis, characterized by rectal bleeding, stool abnormality (diarrhea or constipation), and diffuse mucosal ulceration and friability limited to the rectum or rectosigmoid colon.

**Progress of signs and symptoms**

Inflammation, bleeding and tenesmus usually start to subside within three to five days. Sigmoidoscopic examination after two or three weeks will reveal extent of mucosal improvement and direct subsequent therapy. (Severe cases may require up to three months Cortenema treatment followed by gradually reduced doses until discontinuation.)

**Patient convenience and economy**

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Hydrocortisone enema therapy provides relief of symptoms and mucosal inflammation with minimal concern for steroid side effects. About 30%-50% absorption may occur, but with only transient adrenal suppression reported. Therapy is economical for the patient. The usual three week course costs far less than even one day of hospitalized treatment.

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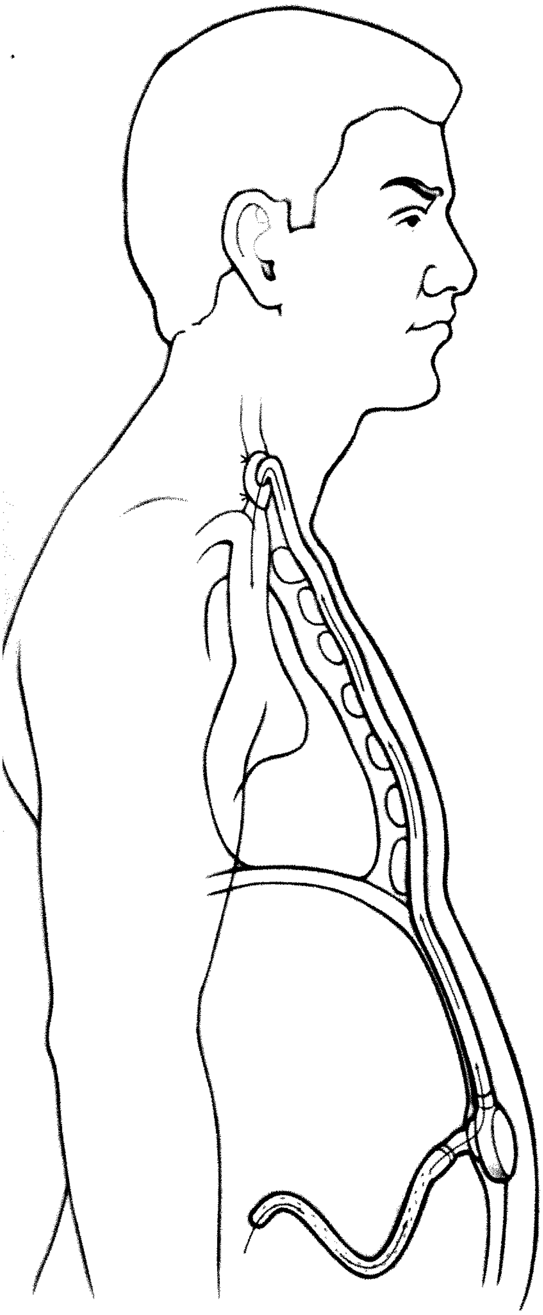
See page opposite for brief summary.

# In refractory ascites the LEVEEN Peritoneo-Venous Shunt can achieve dramatic results



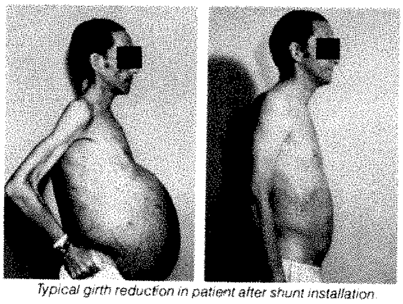
The LEVEEN Peritoneo-Venous Shunt can improve the prognosis of patients with ascites who become refractory to medical measures. It offers significant improvement in the control of ascites and reduces morbidity of such patients. The shunt can be used in ascites of varying origin.

## Removes and prevents fluid buildup

Implanted permanently in a simple surgical procedure, the LEVEEN Peritoneo-Venous Shunt returns peritoneal fluid to the superior vena cava through a pressure-sensitive extra-peritoneal valve. Through continuous reinfusion of the patient's own ascitic fluid, the shunt removes and prevents fluid buildup.

## Clinical experience

Postoperative improvement following insertion of the LEVEEN Peritoneo-Venous Shunt is often dramatic, particularly in the reduction of abdominal girth. Improvement is generally evidenced by: reduced weight, increased urine output, improved renal function, lowered BUN and creatinine levels, reduced aldosterone, elevated plasma protein (with a return of the albumin-globulin ratio toward normal), and greater patient comfort, mobility and ease of breathing. In many patients with marked wasting before surgery, appetite is improved and body mass is regained postoperatively.[1]



*Typical girth reduction in patient after shunt installation.*

**Dramatic relief of symptoms.** To date, the LEVEEN Peritoneo-Venous Shunt has been placed in more than 1,100 patients throughout the world. In one reported series of patients whose serum bilirubin was less than 10mg/100 ml, who had no evidence of severe encephalopathy, and no recent episode of upper gastrointestinal bleeding, 71% were alive 18 months later. At 18 months, these survivors had exceeded the survival rate expected for patients with refractory ascites treated with other accepted methods.[2]

For further information about the LEVEEN Peritoneo-Venous Shunt and its clinical experience, write to Ms. Peggy Harding, Becton, Dickinson and Company, Rutherford, N.J., 07070, or call this toll free number for answers to your technical questions: 800-631-0174. In New Jersey call 201-460-2251.

**The LEVEEN Peritoneo-Venous Shunt.**

**The reinfusion shunt controls ascites through continuous reinfusion of the patient's own ascitic fluid.**

*The LEVEEN Peritoneo-Venous Shunt is an in vivo device containing a unique, one-way valve which permits the unidirectional flow of ascitic fluid from the abdomen to the vascular system whenever the intraperitoneal pressure exceeds the central venous pressure by 3 cm. of water.*

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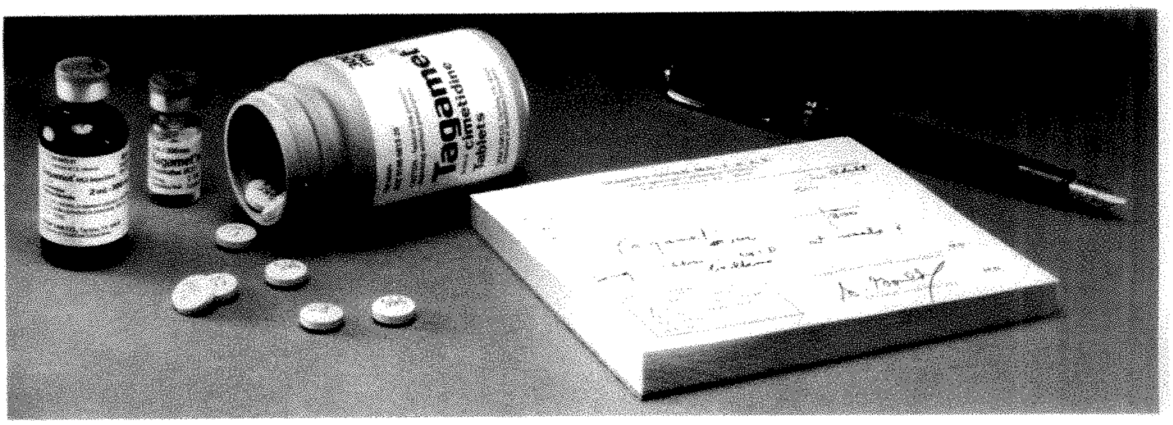

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The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

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Dosage should be reduced in patients with impaired renal function.

**Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.**

**Indications:** 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

**Contraindications:** There are no known contraindications to the use of 'Tagamet'.

**Precautions:** In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

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**Injection:** 300 mg./2 ml. in single-dose vials and in 8 ml multiple-dose vials in packages of 10.

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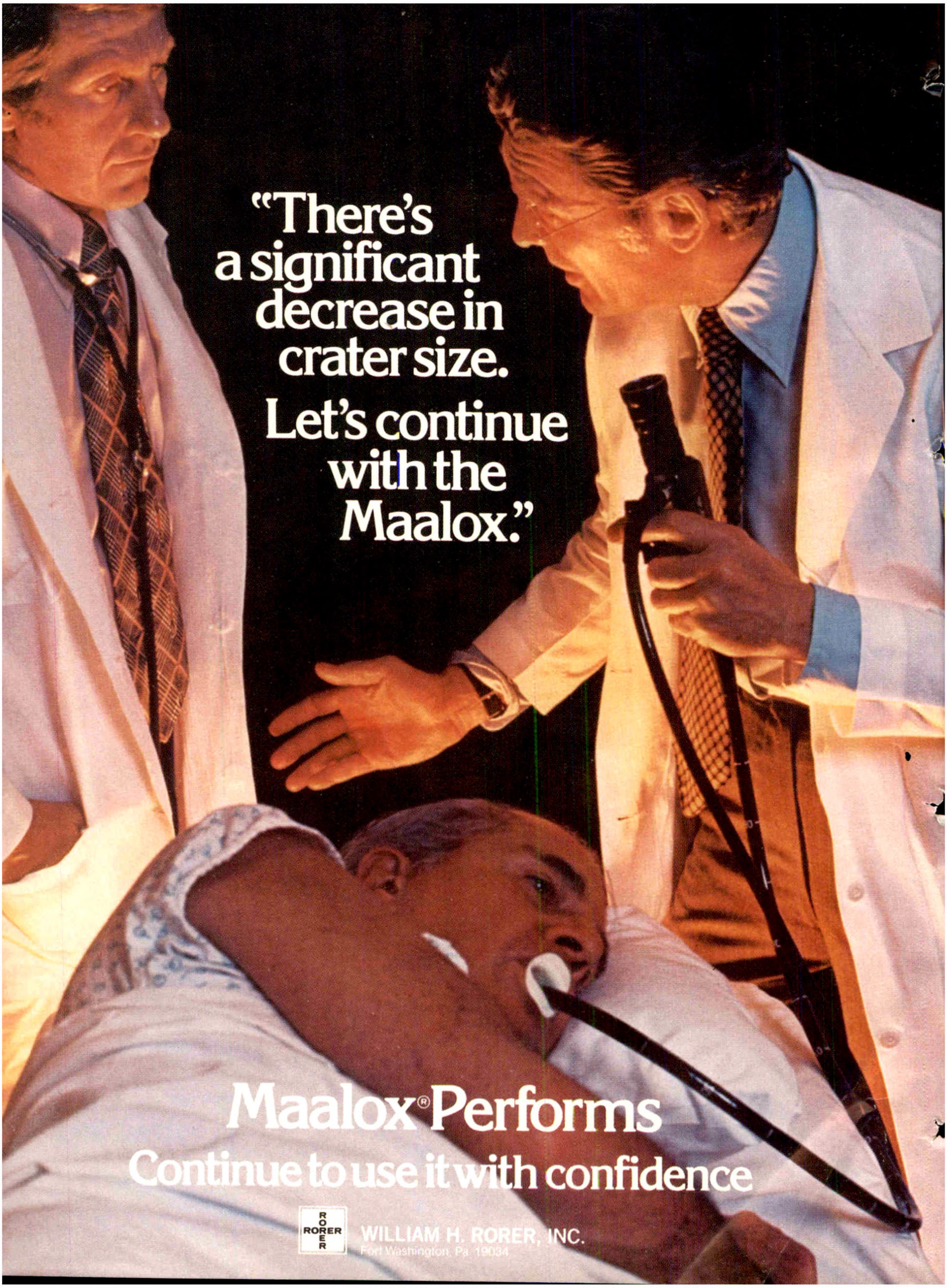
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# Treatment of Irradiation Esophagitis*

## VALUE OF HYDROCORTISONE INJECTION

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Irradiation of the esophagus and mediastinum is performed for a variety of malignant tumors but radiation esophagitis is rarely mentioned in the literature.[1-3] When this type of reaction occurs in its more severe forms, inflammation and scarring ensue with consequent obstruction and dysphagia which may seriously compromise cancer treatment. Irradiation damage to the esophagus and surrounding tissues makes attempts at surgical correction of strictures most hazardous. Medical dilatation, essentially all that is available to overcome the esophageal narrowing and support the patient's nutrition, must be carried over extended periods of time and radiation-induced strictures are sometimes difficult to manage.

At the University of Texas M. D. Anderson Cancer Center, patients with irradiation esophagitis are referred to the gastrointestinal section for management, which must be continued during the patient's lifetime. The problem of keeping the esophagus patent and the patient in good nutrition may be simple or quite complex, depending on the nature and severity of esophageal injury. Most strictures respond to ordinary dilatation but occasionally there is extreme difficulty in maintaining a patent lumen and nutrition becomes inadequate. Because of previous success in overcoming an inflammatory rectal stricture with hydrocortisone injection[4] this procedure was tried in esophageal strictures of several patients with favorable results.

### PATIENT MATERIAL AND METHODS

During a 10-year period, 1 July 1965-1 July 1975, 16 patients with irradiation

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* Read before the 42nd Annual Convention of the American College of Gastroenterology, New Orleans, LA, 24-26 October 1977.

† The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute.

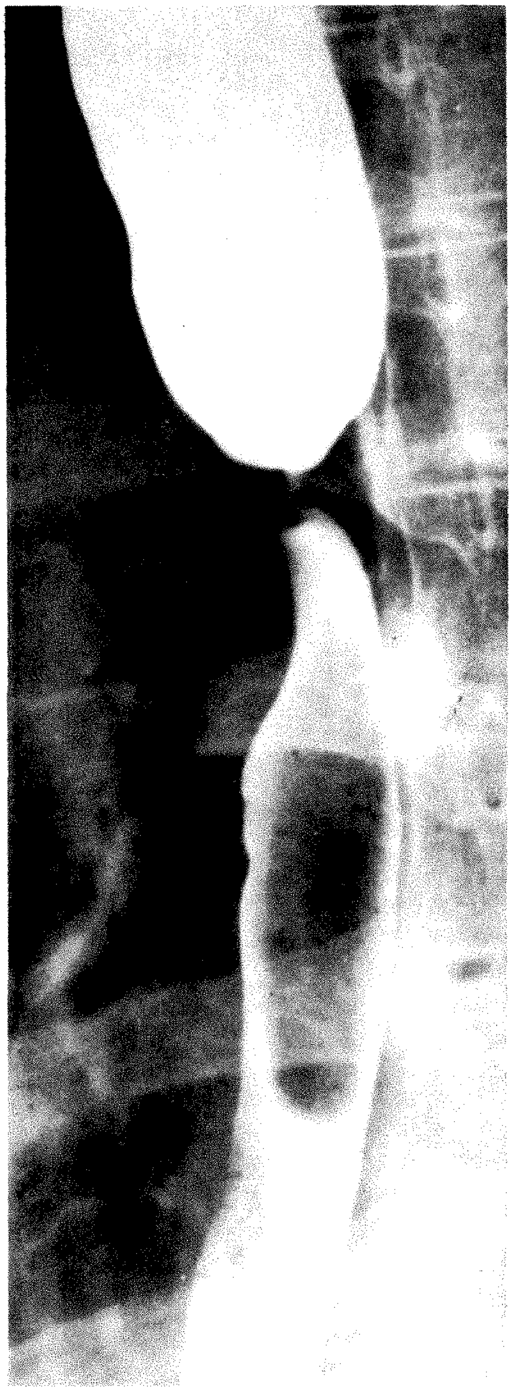

Fig. 1a—Esophagogram demonstrates a marked area of focal narrowing in the mid esophagus with proximal dilatation (Patient 8, Table I).

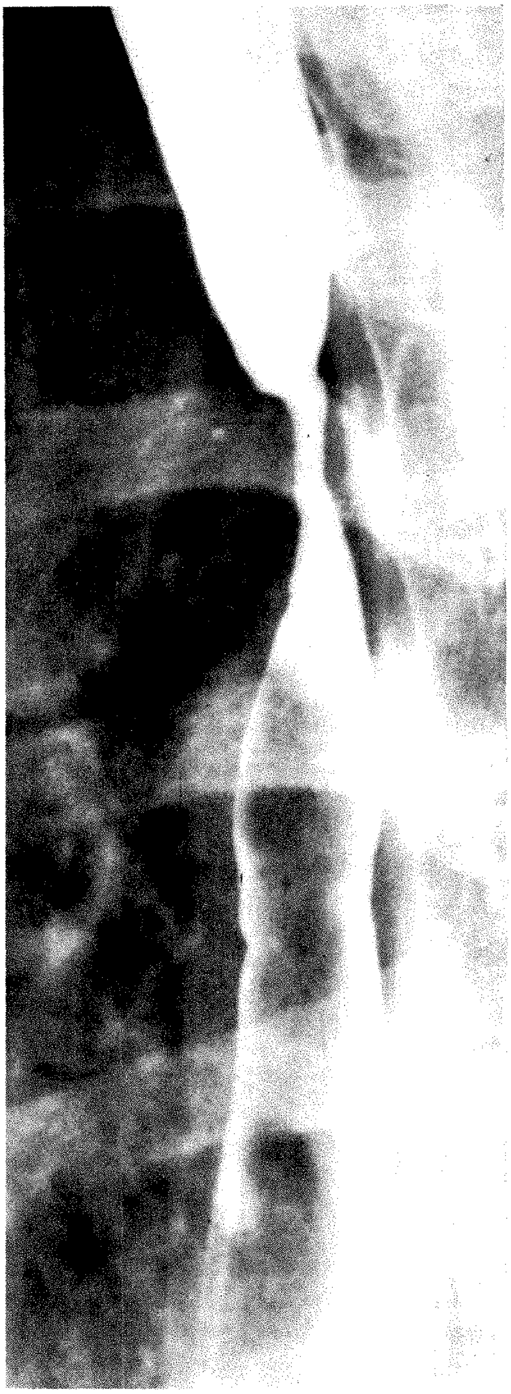

Fig. 1b—Repeat barium examination demonstrates increased luminal caliber of the mid esophageal stricture after hydrocortisone injection and dilatation.

esophagitis were seen on the gastroenterology service of The University of Texas M. D. Anderson Hospital and Tumor Institute. All had received irradiation to the mediastinum, varying from 3,000 to 6,000 rads. There were eight with carcinoma of the lung, three with Hodgkin's disease and one each with histocytic lymphoma, embryonal cell carcinoma, transitional cell bladder cancer, squamous carcinoma of the neck and squamous carcinoma of the esophagus.

Each patient was evaluated by roentgenography and esophagoscopy. For the latter, the Olympus E Fiberesophagoscope was used. Initial dilatations were invariably with the Eder-Puestow dilator, often followed by either the Hurst or Maloney mercury-filled instruments. Hydrocortisone injection was performed by passing the Olympus injection needle through the biopsy channel of the fiberscope, advancing the needle and injecting 25 mg. of hydrocortisone in each of four opposite sites around the mouth of the stricture opening, followed by re-dilation within 24-48 hours. Excellent follow-up was obtained in all patients.

## RESULTS

Evaluation of patients with irradiation injury showed that four had motility disorders only, nine had inflammation, ulceration or both, plus narrowing or stricture and three had well-developed strictures without evident inflammation. Dilatation was performed repeatedly in 10/16 patients; 1/4 with motility disorders, 6/9 with inflammation, narrowing, or stricture and 3/3 with developed strictures. All but one dilated showed definite improvement and nutrition was well maintained on oral feedings. There was one perforation in a patient with a tight stricture with small abscess formation. This was surgically drained and after recovery the stricture was successfully dilated following hydrocortisone injection (Figs. 1a and 1b).

Hydrocortisone injection was confined to those patients with tight strictures which proved refractory to standard dilatation technic, five in all. These responded with improved maintenance of dilation, ease of swallowing and better nutrition. The injection was repeated several times in each case but resulted in eventual sustained dilation so that in most instances ordinary dilatation could be continued on a routine basis, usually with a Maloney mercury-filled dilator (Table I).

## COMMENT

There is little doubt that radiation esophagitis occurs, despite the few references in the literature. Seaman and Ackerman, in an excellent presentation of their own results and discussion of the literature, point out that the damage in most cases is light but may be severe in hypersensitive individuals.[5]

Irradiation-induced injury to the esophagus may have a variety of roentgenological appearances which often correlate well with endoscopy. The majority of patients who have symptoms following completion of mediastinal irradiation demonstrate no morphologic findings on esophagography. Abnormal motility is the most frequent radiologic finding encountered in our experience.[6] The altered motility is characterized by failure to complete the primary peristaltic wave which is usually disrupted at about the proximal level of mediastinal irradiation. Frequently, tertiary contractions are noted in the esophagus as well as intermittent failure to relax the distal esophageal sphincter. When esophageal strictures occur, quite typical benign radiologic characteristics are present with smooth, tapering margins and no particular irregularity within the area of narrowing.

TABLE I

| Patient | Sex | Age | Diagnosis | XRT | X-ray | Endoscopy | Treatment | Results |
|---|---|---|---|---|---|---|---|---|
| 1. | F | 61 | Ca lung | 6,028r | Stricture and ulcer | Esophagitis and stricture | Dilation | Died: necrotizing esophagitis. |
| 2. | M | 62 | Ca lung | 6,000r | Esophagitis | Esophagitis | None necessary | Died: generalized disease. |
| 3. | F | 45 | Hodgkin's disease | 6,000r | Motility disorder | Esophagitis narrowing | Antacids<br>No dilation | Recovered on treatment. |
| 4. | F | 62 | Ca lung | 6,000r | None | Esophagitis ulceration and stricture | Dilation<br>Hct inj. | Good. died of disease. |
| 5. | M | 35 | Embryonal cell Ca | 6,000r | Esophagitis stricture | Esophagitis stricture | Dilation | Good. Died of disease. |
| 6 | F | 82 | Squamous Ca esophagus | 5,000r | Esophagitis stricture | Esophagitis stricture | Dilation<br>Hct. inj. | Good. On follow-up. |
| 7. | F | 58 | Ca lung | 6,000r | Motility disorder | Motility disorder | None | Good. Died of disease. |
| 8. | F | 26 | Hodgkin's disease | 3,000r | Esophagitis stricture | Esophagitis stricture | Dilation<br>Hct. inj. | Perforation with recovery improved. |

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TABLE *(continued)*

| Patient | Sex | Age | Diagnosis | XRT | X-ray | Endoscopy | Treatment | Results |
|---|---|---|---|---|---|---|---|---|
| 9. | M | 60 | Ca lung | 3,000r | Esophagitis stricture | Esophagitis stricture | None | Tracheo-esophageal fistula: died. |
| 10 | M | 64 | Ca bladder | 6,000r | Motility disorder | Motility disorder | Dilation | Poor. Died after gastrostomy |
| 11. | F | 50 | Ca lung | 4,500r | Motility disorder | Not done | None | Good. Died of disease. |
| 12. | F | 58 | Ca lung | 5,000r | Esophagitis stricture | Not done | None | Poor. Died of disease. |
| 13. | F | 66 | Ca lung | 5,000r | Esophagitis stricture | Esophagitis stricture | Dilation<br>Hct. Inj. | Good. On treatment. |
| 14. | M | 52 | Ca neck metastatic | 6,400r | Esophagitis stricture | Esophagitis stricture | Dilation | Improved. Died of disease. |
| 15. | M | 13 | Histiocytic lymphoma | 4,000r | Esophagitis stricture | Stricture | Dilation<br>Hct. Inj. | Good. On treatment. |
| 16. | F | 24 | Hodgkin's disease | 4,000r | Esophagitis stricture | Stricture | Dilation | Good. Died of disease. |

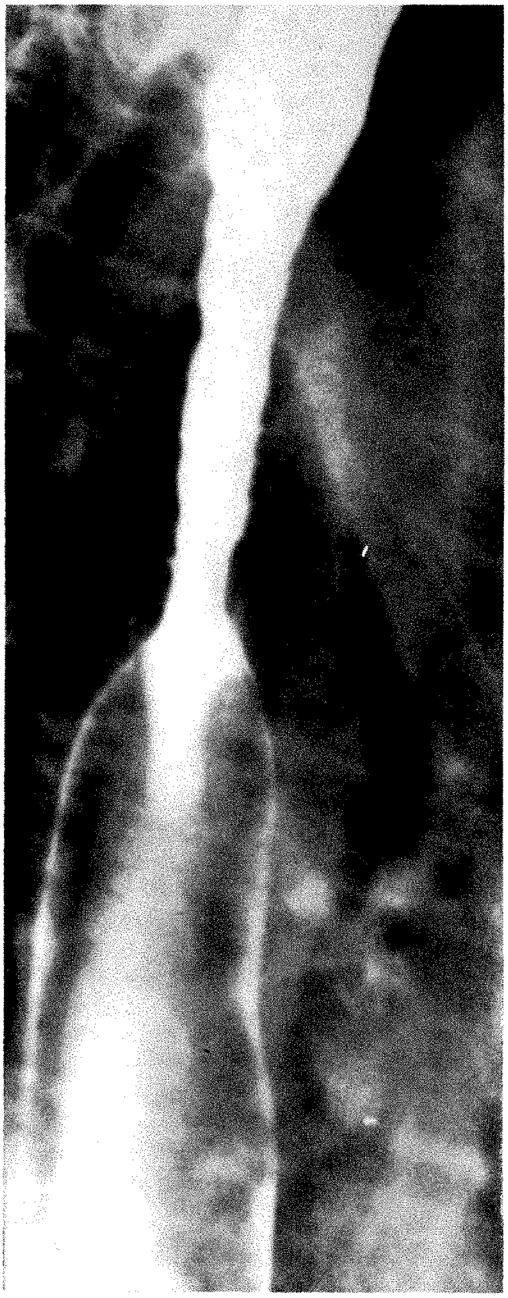

Fig. 2—An elongated stricture is present in the mid thoracic esophagus at the level of the irradiation ports. Small serrations are present in the narrowed area probably indicating tiny ulcerations. Injection of hydrocortisone around narrowed distal area resulted in better dilation and improved nutrition (Patient 13, Table I).

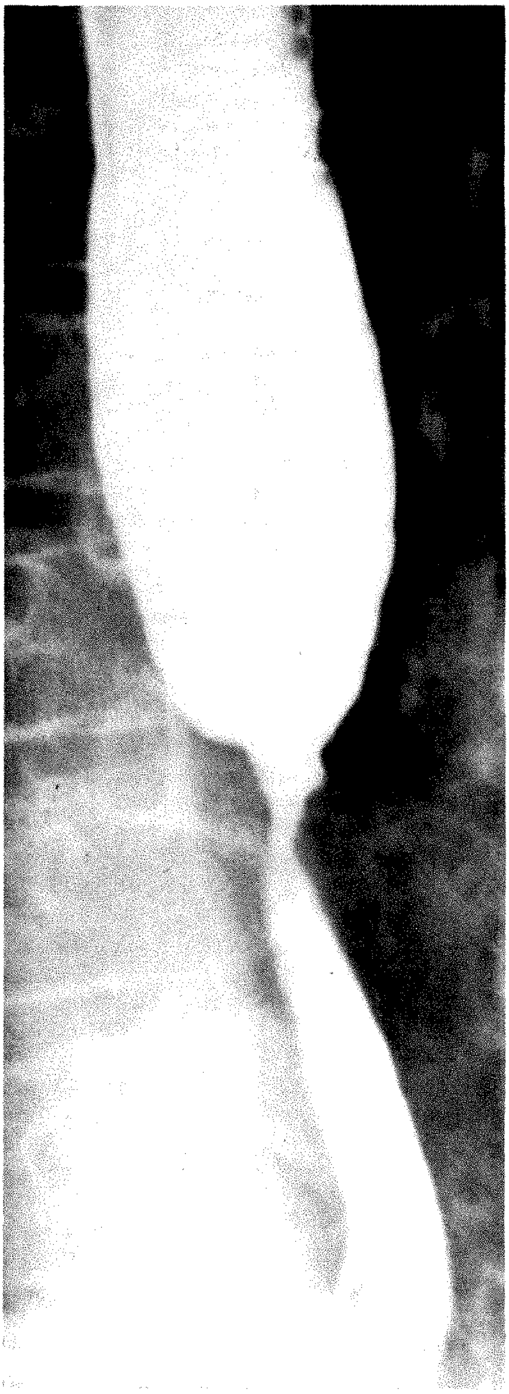

Fig. 3—Esophagram shows a focal stricture of the distal third of the thoracic esophagus with some proximal obstruction (Patient 15, Table I). Patient became asymptomatic after hydrocortisone injection and dilatation.

Varying degrees of obstruction may be associated (Figs. 2 and 3). Frank ulceration at the site of irradiation has been the least commonly observed radiologic feature.

Acute injury is apparently manifested by mucosal degeneration and infiltration of the submucosa and muscularis. The latter may show severe degeneration in resected human esophagi.[5] There is later complete regeneration of mucosa, even when severe stricture formation occurs but submucosal and muscular changes persist. There is evidence that such changes may be enhanced by the administration of Adriamycin during radiation therapy.[8] The massive thickening and degeneration may well be the cause of the extreme difficulty in dilatation of some irradiation strictures.

The effect of hydrocortisone injection on the lesions is unknown. Clinically, however, we have observed that dilation after steroid treatment is easier and seems to be maintained longer in cases previously resitant. The technic is relatively simple for the trained endoscopist, has been attended with no complications even when repeated several times, and is thus easily added to dilatation.

Dysphagia is common following high doses of irradiation to the mediastinum. There are apparently no endoscopic studies in the great majority of such patients unless symptoms persist. Careful esophagoscopic follow-up of patients who are seriously symptomatic might help to clarify the sequence of mucosal abnormalities. Trials of systemic steroids in such cases could then be made when changes are massive and persistent, with the objective of preventing stricture formation. Studies of this type obviously would require close cooperation between the radiotherapist and gastroenterologist but would certainly add to the knowledge of this type of radiation injury. At the very least, patients with developing strictures could be subjected to treatment earlier and severe malnutrition prevented.

## ADDENDUM

Since summarizing statistics for this paper, an additional two patients with radiation esophagitis and three with peptic esophagitis and stricture have been treated with hydrocortisone injection. Results have been good to excellent.

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*Texas Med Ctr.*
*Houston, TX 77030*

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# Esophageal Achalasia Secondary to Gastric Carcinoma

## REPORT OF A CASE AND A REVIEW OF THE LITERATURE

RICHARD W. McCALLUM, M.B., B.S., F.A.C.G
New Haven, CT

A case of invasive gastric carcinoma mimicking idiopathic achalasia radiologically, endoscopically and manometrically is described. This is only the second case of tumor-associated achalasia with a positive mecholyl test where there was no demonstrable histological tumor involvement of the myenteric plexus in the body of the esophagus. The interpretation of the manometric findings including the positive mecholyl test are discussed in the light of these histological findings. The short duration of symptoms, the presence of anemia and guaiac positive stools, along with subtle radiologic abnormalities of the gastric fundus were aspects of this case which should increase the index of suspicion and lead to the correct diagnosis. In the evaluation of patients with the achalasic syndrome, a tumor-associated functional and organic disorder mimicking idiopathic achalasia in all respects has to be considered.

Achalasia, or cardiospasm, is a motor disorder of the esophagus with a characteristic clinical and radiologic presentation.[1] The diagnosis is best established by esophageal manometry. The lower esophageal sphincter pressure is usually higher than normal with incomplete relaxation in response to swallowing and low amplitude nonperistaltic esophageal contractions in the body of the esophagus.[2] In addition, there is an increased sensitivity of the body of the esophagus to parenterally administered methacholine (acetyl-B-methyl chloride or mecholyl).[3, 4]

Carcinoma of the gastric fundus encroaching on the gastroesophageal junction can, on very infrequent occasions, result in a clinical presentation[5] and radiologic pattern indistinguishable from that of primary achalasia.[6] In rare cases of gastric fundal carcinoma, the esophageal manometric findings, including a positive mecholyl test, have mimicked primary achalasia.[7-10]

This report describes a patient who, by clinical, radiological, endoscopic and manometric criteria, was indistinguishable from achalasia but who had a gastric adenocarcinoma infiltrating and obstructing the gastroesophageal junction. In this patient, the myenteric plexus in the body of the esophagus had no histological evidence of destruction. The approach to this diagnostic dilemma is discussed and the literature reviewed, along with speculation on the pathogenesis of this presentation of gastric carcinoma.

### CASE REPORT

A 54-year old white male was admitted to the Wadsworth Veterans Administration Hospital and UCLA in February, 1976 with a 12-month history of increasing painless dysphagia, nocturnal regurgitation of fluids and a 9 kg. weight loss. An upper gastrointestinal series, that had been ordered by his family physician in February, 1975,

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From the Medical Service, Wadsworth Veterans Administration Hospital Center and the Department of Medicine, UCLA Center for the Health Sciences, Los Angeles.

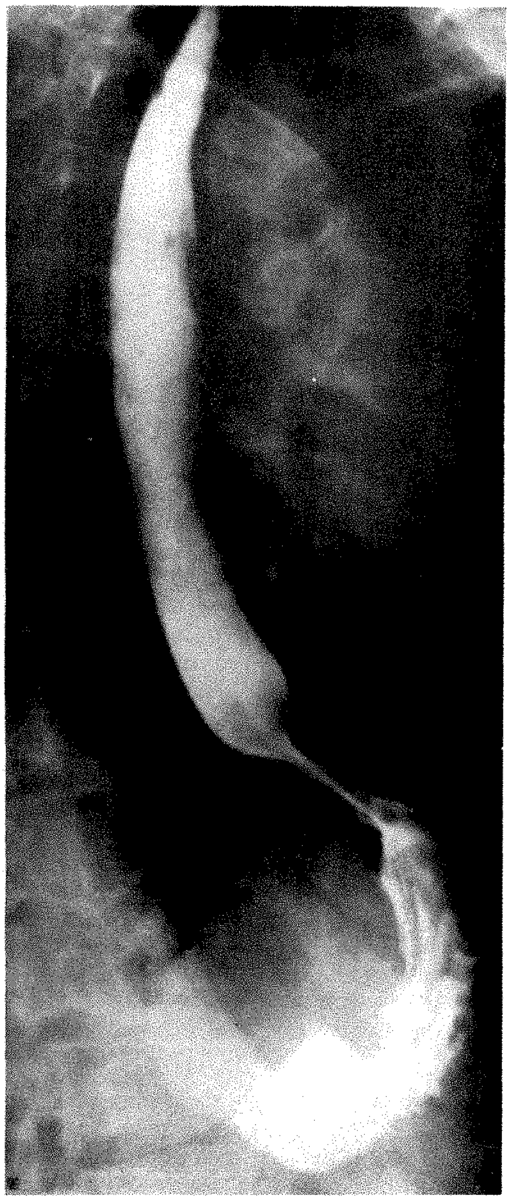

Fig. 1—A representative film from the upper gastrointestinal series performed one year prior to the diagnostic motility study showing a normal appearing esophagus and stomach.

after approximately three weeks of dysphagia, was within normal limits (Fig. 1) but upper gastrointestinal endoscopy and radiology three months later were consistent wih the diagnosis of achalasia. Over the subsequent nine months prior to presenting at UCLA, the patient had received two pneumatic dilatations and numerous dilatations with a Hurst bougie with only transitory symptomatic improvement. A repeat upper gastrointestinal endoscopy was reported as being consistent with the diagnosis of achalasia, in that the endoscope could be passed into the stomach and no lesions were visible in the region of the gastroesophageal junction. The patient gave no past history of heartburn, esophageal problems, or past surgery of the stomach or esophagus.

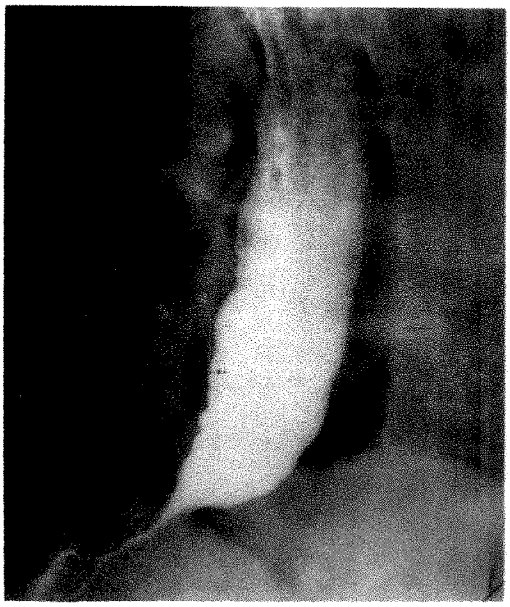

Fig. 2—The esophageal lumen is moderately dilated with retained food particles and tertiary contractions present. The lower esophagus terminates in a smooth narrowing typical of achalasia. On closer examination, there is deformity of the fundal contour and some irregular streaming of barium as it flows into the stomach, suggesting encroachment by a fundal mass.

On examination, the patient was a thin, chronically ill-appearing white male, whose physical examination was negative, except for 3+ guaiac positive stool. Hemoglobin was 12.0 gm.%. An upper gastro-

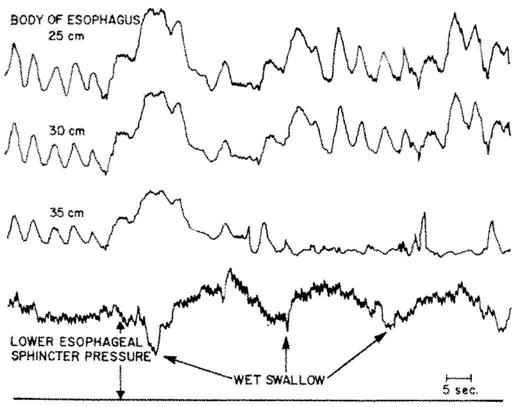

Fig. 3—Esophageal motility tracing showing simultaneous contractions in the body of the esophagus with a hypertensive lower esophageal pressure of 40-45 mm. Hg. Following wet swallows, there is inadequate and incomplete relaxation (< 50%) of the lower esophageal sphincter.

intestinal series on admission showed marked dilatation and aperistalsis of the body of the esophagus and a smooth tapered narrowing at the gastroesophageal junction of maximal diameter only 3 mm. (Fig. 2). Esophageal motility studies, using a constant perfusion technic, were diagnostic of achalasia[2] (Fig. 3). The lower esophageal sphincter pressure was 40-45 mm. Hg. with < 50% relaxation with wet swallows. There were low amplitude nonperistaltic contractions of the distal two-thirds of the body of the esophagus accompanying every swallow. Intraesophageal pressure was 10 mm. greater than intragastric pressure. Mecholyl (7.5 mg.) subcutaneously produced a positive response,[4] with increased spontaneous activity and a 30 mm. Hg. elevation of baseline pressure in the body of the esophagus (Fig. 4).

Despite two technically successful pneumatic dilatations, he did not improve symptomatically, or by radiologic or manometric criteria. Over the previous one month, two hard subcutaneous mobile nodules, 1-2 cm. in diameter, were noted on the chest and pubic area. Biopsy of these nodules revealed metastatic adenocarcinoma. Because of the possibility of carcinoma, despite the two previous negative endoscopies, the patient was re-endoscoped with an Olympus Type D forward viewing fiberoptic panendoscope. The endoscope (French size 34) could not be passed into the stomach. There was marked friability of gastroesophageal junction, particularly at an area of nodularity present on the anterior gastroesophageal wall. The biopsies of the lesion showed moderately well differentiated adenocarcinoma. A careful review of the upper gastrointestinal series, performed on admission to UCLA, raised the question of a fundal mass because of deformity of the fundal contour and irregular barium flow into the stomach (Fig. 2).

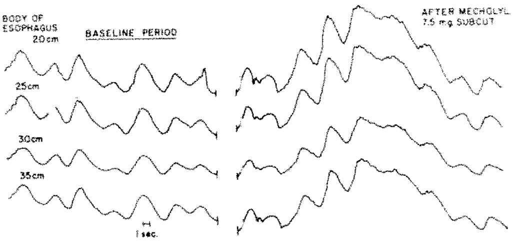

Fig. 4—Positive methacholine (mecholyl) test with the baseline period shown on the left and then a demonstratable rise in pressure of greater than 25 mm. Hg. following 7.5 mg. subcutaneous mecholyl shown on the right. The mecholyl response evolved over several minutes and only the diagnostic final part is shown on the right.

At surgery he was found to have a large tumor of the gastric fundus invading the gastroesophageal junction, diffuse liver metastases and tumor involvement of the left lower lobe of the lung. Resection was impossible and an end-to-side esophagojejunostomy was performed with anastomosis a few centimeters above the gastroesophageal junction. A tissue specimen from the proximal esophageal margin was obtained. Microscopic examination showed no evidence of malignancy and, specifically,

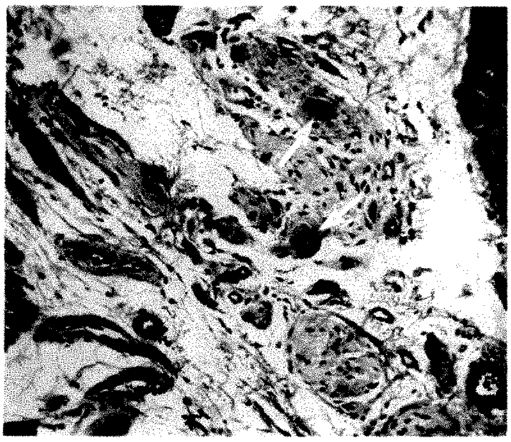

Fig. 5—The myenteric nerve plexus is depicted and two ganglion cells are identified (note arrows). There is no evidence of tumor invasion. Other sections of the musculara externa also showed no tumor infiltration.

no tumor invasion of the myenteric plexus with normal ganglion cells (Fig. 5). After a satisfactory postoperative period, chemotherapy was begun. An EMI head scan showed orbital metastases. The patient died six months after surgery from diffsue metastases. No autopsy was performed

## COMMENT

Carcinoma of the gastroesophageal junction or gastric cardia extending into the esophagus can radiologically produce smooth narrowing of the area involved, an appearance indistinguishable from that of idiopathic achalasia.[6, 11, 12] When esophageal achalasia is suggested clinically and radiographically, esophageal manometric studies are relied on to establish the diagnosis.[2] Intraluminal esophageal manometric recordings have been performed in patients with a known diagnosis of adenocarcinoma of the gastric cardia invading the distal esophagus but not radiologically mimicking achalasia.[8-13] Lower esophageal sphincter pressure was abnormally low in the majority of cases and normal in the remainder. The finding of decreased sphincter function was attributed to rigidity, resulting from tumor infiltration of the gastroesophageal junctional area. In addition, the deglutitive pressure patterns in the body of the esophagus of these patients revealed simultaneous nonperistaltic responses in the majority of cases, with high amplitude and prolonged duration of the contractions. This diffuse esophageal spasm pattern has been previously reported in association with gastric carcinoma[14] and was regarded as representing a response of the esophagus to distal obstruction. There is nothing specific in this pattern, since a functional hypertensive lower esophageal sphincter can produce similar findings.[15]

The patient in this case report presented with objective evidence of achalasia within one year of becoming symptomatic. The possibility that carcinoma was superimposed on a long-standing and asymptomatic achalasia has to be considered. In the most comprehensive review of the topic, the incidence of esophageal malignancy in achalasia varied from 1-20%[16] and occurred with a long-standing history ranging from eight to 33 years.[1, 17, 18] The most common site of origin was the middle third, thought to correlate with the upper level of stasis esophagitis and food retention and the predominant histologic type was squamous cell.[16] Thus, the evidence in this patient is against malignancy superimposed on previous achalasia; and, in addition, a normal upper gastrointestinal series was available at the onset of symptoms one year preceding the diagnostic motility study.

In the reported cases of gastric carcinoma producing achalasia, documented by manometric studies and a mecholyl test,[7, 9, 10] carcinomatous involvement of the esophageal myenteric plexus has been accorded a principle role in the pathogenesis and there has been well documented histologic involvement of the myenteric plexus. In the present case, tumor invasion of the myenteric plexus at the squamocolumnar junction was assumed because of the unresectibility of the lesion at this site. Despite the presence of advanced motor failure within the body of the esophagus, there was no histological evidence of tumor involvement of the myenteric plexus in the surgical specimen from the distal esophagus. The present case represents only the second ever documented of tumor associated achalasia with a positive mecholyl test and no involvement of the myenteric plexus in the body of the esophagus.[9]

What then is the genesis for the achalasia-like picture and mecholyl response in this case? The majority of cases of well established idiopathic achalasia have histopathological evidence of the absence of ganglion cells.[19] Cassella and associates found that 32% of patients with typical idiopathic achalasia had only minor changes in the myenteric plexus.[20] In all these, however, electron microscopy showed the changes suggestive of the Wallerian type of degeneration in their vagal nerve fibers and in two patients, at autopsy, there was a greatly reduced number of ganglion cells in the dorsal motor nucleus. They proposed that the primary site of the disease process in achalasia was the neural pathways extrinsic to the esophagus and that, with time, this disorder led progressively to loss of myenteric cells and denervation of the lower two-thirds of the esophagus. Hence, the primary functional disorder in the present case may have been at the level of the dorsal motor nucleus of the vagus from widespread metastases; from a bilateral thoracic vagotomy by local tumor infiltration; or at the level of the esophageal myenteric plexus by tumor not appreciated by light microscopy of the biopsy specimen.

There are some instructive clinical and radiologic aspects of this case. The patient, in the latter part of his course, had guaiac positive stools and was anemic, both of which are distinctly unusual in idiopathic achalasia[21] but common in gastric carcinoma. In the face of clinical, radiologic and manometric refractoriness to well performed pneumatic dilatations, a careful review of the radiographs for previously discussed subtle abnormalities suggesting a fundal mass are indicated. Also, a repeat esophagogastric endoscopy should be considered to re-examine the gastric fundus. Cytology should be included since esophageal carcinoma can be diagnosed by cytologic study, even when other tests have been negative.[22, 23] It is concluded that, in the evaluation of patients with the achalasia syndrome, a tumor-associated functional and organic disorder, which can mimic idiopathic achalasia in all respects, has to be considered and carefully excluded.

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# Gastrointestinal Bleeding in Aortic Stenosis

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Gastrointestinal bleeding in aortic stenosis is an uncommon condition but when present it is often undiagnosed. The usual radiological proceedures fail to demonstrate the source of bleeding. Mesenteric angiography, however, will identify the lesion. The lesion is usually a vascular malformation located in the right colon. The angiodysplasia may also occur in other parts of the gastrointestinal tract.

We have encountered five patients with aortic stenosis who had multiple massive hemorrhages of the lower gastrointestinal tract who defied diagnosis by the conventional methods. Mesenteric angiography, however, disclosed the orgin of the bleeding. In four patients vascular malformations were found in the right colon and one in the jejunum. Right hemicolectomy and partial jejunectomy resulted in a cure in all.

The controversy whether patients with aortic stenosis are more prone to cryptogenic hemorrhage than the population at large has made appropriate diagnosis and treatment difficult. Usually appearing in patients of advanced age, the often massive and recurrent bleeding presents a difficult problem to both patient and physician. The issue is further compounded by the common administration of multiple transfusions causing further compromise of the patient's cardiac status. Limited awareness regarding the possible coexistence of these two entities has made adequate diagnosis by the use of angiography infrequent.

Between February, 1973 and July, 1976 five patients with typical aortic stenosis who had massive recurrent gastrointestinal hemorrhage were treated at University, Bellevue and Booth Memorial Hospitals. Angiographic study demonstrated vascular malformations in the right colon in four and in the jejunum in one. Right hemicolectomy and partial jejunectomy resulted in a cure in all five patients.

## CASE REPORTS

*Case 1:*—O. B., a 65-year old white female was admitted to University Hospital for a fifth episode of asymptomatic bright red bleeding from the rectum within the past two years. Seventeen pints of

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From the Department of Medicine and Radiology of New York University Medical Center.

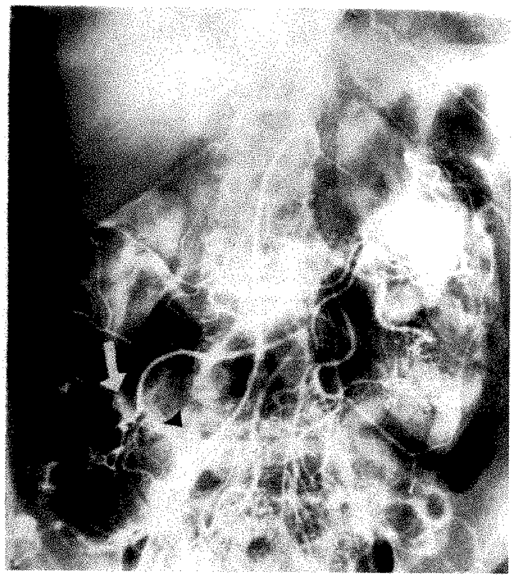

Fig. 1—Case 1, superior mesenteric angiogram midarterial phase. A small area of abnormal vascularity is noted in the cecum (arrowhead). In the same region an early draining vein fills (arrow) during the arterial phase of the injection. The vascularity of the remainder of the bowel is normal.

blood were required during four previous admissions. Upper and lower gastrointestinal radiographic studies as well as upper panendoscopy and colonoscopy had been consistently normal.

Her past history revealed acute rheumatic fever in adolescence and detection of aortic stenosis in adulthood.

The physical examination at this admission revealed pallor of the skin and mucous membranes and a grade IV/VI basilar ejection systolic murmur radiating to the neck on the right side. The rhythm was regular and the blood pressure was 145/86. There were no other significant findings.

Laboratory data revealed an iron deficiency anemia with a hematocrit of 25% and hemoglobin of 5 gm.%.

The electrocardiogram showed left ventricular hypertrophy and the chest x-ray demonstrated an increased transverse diameter of the heart in addition to calcification in the region of the aortic valve.

Once again barium x-rays of the upper and lower tracts were normal. Abdominal angiography, however, demonstrated the presence of angiodysplasias in the cecum and ascending colon (Fig. 1).

Four units of packed cells were administered prior to preparation for surgery. A right hemicolectomy was performed without incident. No further bleeding was noted during a two-year follow-up period.

*Case 2:*—A. W., a 65-year old white female was admitted to the Booth Memorial Medical Center because of fatigue of three months' duration. There were five previous admissions within the past five years because of asymptomatic melena. Barium radiographic studies of both upper and lower tracts including repeated sigmoidoscopic examinations failed to reveal the source of the bleeding.

Physical examination revealed marked pallor of the skin and mucous membranes. The heart was enlarged to the left and a grade IV/VI ejection systolic murmur was heard at the aortic area. The rhythm was regular and the blood pressure was 160/90. The rest of the examination was not significant.

An hypochromic anemia (Hct., 26%; Hgb., 6 gm.) and several positive stool examinations were noted. The electrocardiogram showed evidence of left ventricular hypertrophy and the chest x-ray revealed the presence of calcification in the region of the aortic valve and enlargement of the heart in the transverse diameter.

Barium studies of the upper and lower tracts were nonrevealing but abdominal angiographic studies demonstrated multi-

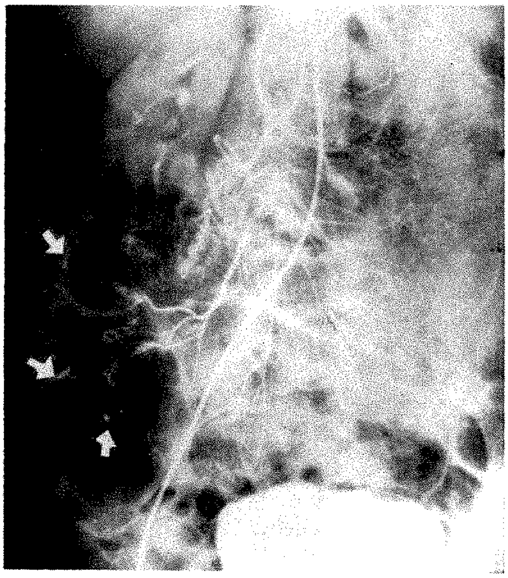

Fig. 2—Case 2, superior mesenteric angiogram shows multiple angiodysplasias in the cecum and ascending colon (arrows).

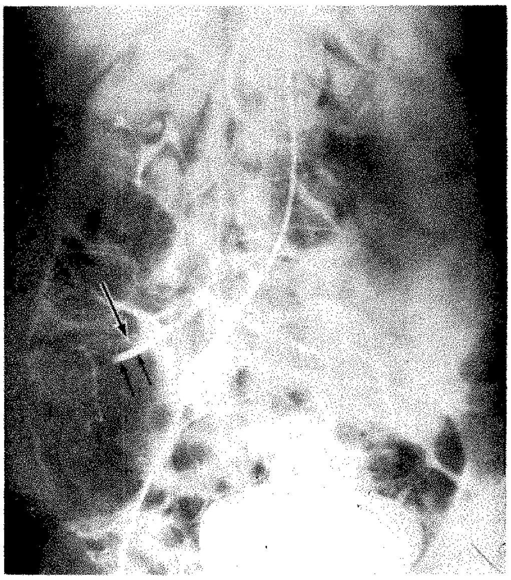

Fig. 3—Case 2, in the capillary venous phase a large dense vein is visible (arrows).

ple angiodysplasias in the cecum and ascending colon (Fig. 2). In the capillary venous phase an early filling of a large dense vein is visible (Fig. 3).

She was given five units of packed cells after which a right hemicolectomy was performed. There has been no evidence of recurrent bleeding in the ensuing two-year follow-up period.

*Case 3:*—B. R., a 79-year old white female was admitted to the Booth Memorial Medical Center because of her eighth episode of having passed profuse amounts of dark red blood per rectum. The cause of the bleeding had never been determined despite repeated upper and lower gastrointestinal radiographic studies. She had known hypertension for 30 years.

Her physical examination revealed pallor of the skin and mucous membranes in addition to a loud aortic systolic ejection murmur which was heard at the base of the heart and radiated to the neck. The heart appeared to be enlarged to the left on percussion and the rhythm was regular. The blood pressure was 180/100. The laboratory data revealed a hypochromic anemia (Hct., 27%; Hgb., 7 gm.) and guaiac positive stools.

The left ventricular hypertrophy was confirmed both on chest x-ray and electrocardiogram.

The upper and lower barium radiographic studies of the gastrointestinal tract failed to identify the source of bleeding. The celiac and superior mesenteric angiograms, however, demonstrated angiodysplasias to be present in the cecum and ascending colon (Fig. 4). Microscopic section of the cecum showed multiple angiodysplastic vessels in the submucosa (Fig. 5).

After receiving four units of packed cells the patient underwent a right hemicolectomy which resulted in the prompt cessation of the bleeding.

She died two years later because of her underlying heart disease and without

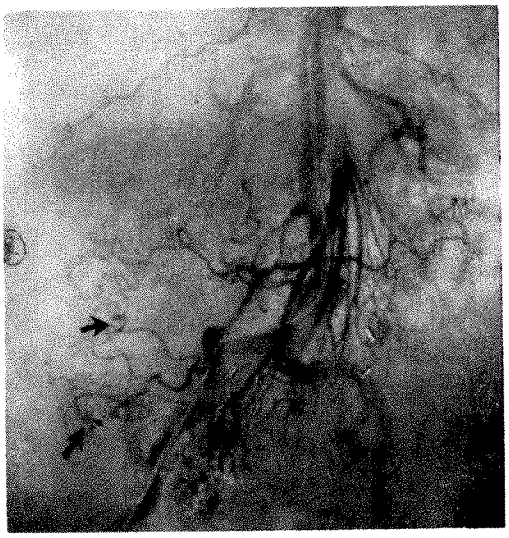

Fig. 4—Case 3, coeliac and superior mesenteric angiogram (arterial phase). The ileocolic artery feeds a small area of abnormal vascularity in the cecum (lower arrow) and ascending colon (upper arrow).

ever having rebled from her gastrointestinal tract.

*Case 4:*—H. L., a 74-year old white male was admitted to University Hospital with a fourth episode of having had asymptomatic dark red blood per rectum. Eleven units of packed red cells had been given during the previous admissions. Barium radiographic studies as well as colonoscopy failed to demonstrate the bleeding site.

The significant physical findings on examination included pallor of the skin and mucous membranes and a grade IV/VI basal ejection systolic murmur which radiated to the carotid arterties. Atrial fibrillation was present and the blood pressure was 110/84.

There was a hypochromic anemia (Hct., 22%; Hgb., 6 gm.) and the stools were guaiac positive.

The chest x-ray showed an increase in the transverse diameter of the heart and the electrocardiogram demonstrated left ventricular hypertrophy and atrial fibrillation.

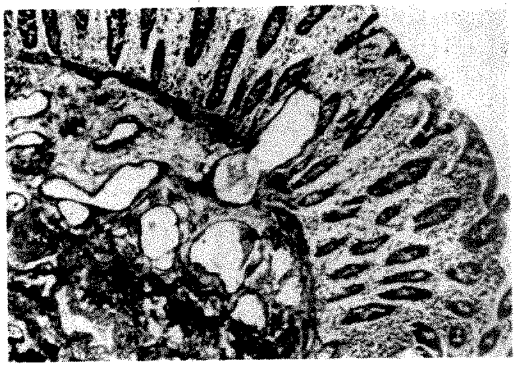

Fig. 5—Miscroscopic section of the cecum showing multiple angiodysplastic vessels in the submucosa. There is one dysplasia that extends into the mucosa.

Barium studies of the upper and lower tracts were normal but abdominal angiography revealed a vascular malformation in the jejunum which was resected (Fig. 6). The resected portion of the jejunum was injected with a gelatin mixture. An abnormal blush was seen in the bowel wall and a large vein draining the malformation was apparent (Fig. 7).

*Case 5:*—F. T., a 90-year old white male was admitted to Bellevue Hospital for the seventh time in four years because of asymptomatic melena and anemia. During these many admissions he was given 30 units of blood, both packed cells and whole blood. He was found to have calficic aortic stenosis with anemia but was never in frank congestive heart failure. Repeated radiographic and endoscopic examination failed to reveal the source of bleeding.

Physical examination on this admission revealed an elderly gentleman in acute distress. He was markedly pale and dyspneic with evidence of recent weight loss. The essential findings in addition to the above were evidence of cardiac enlargement; an ejection systolic murmur at the base radiating to the neck; regular sinus

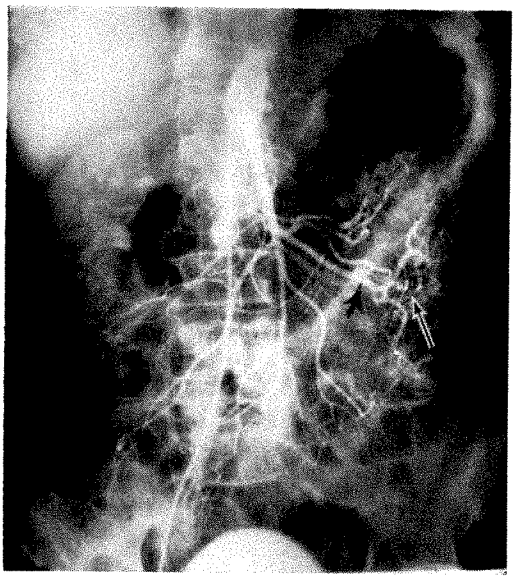

Fig. 6—Case 4, superior mesenteric angiogram (arterial phase). There is enlargement of the fourth jejunal branch artery (left arrow). Arising from this vessel are several dilated tortuous arterial branches (right arrow).

rhythm with mild tachycardia; blood pressure, 110/80 and rales at both bases.

The laboratory findings consisted of Hct., 30%; Hgb., 8 gm. The SMA-12 and urinanalysis were normal. An x-ray of the chest revealed evidence of congestive failure and enlargement of the heart in the transverse diameter.

An electrocardiogram was consistent with left ventricular hypertrophy.

An upper and lower gastrointestinal series as well as endoscopy failed to reveal a source of bleeding. Superior mesenteric angiography demonstrated the presence of a vascular dysplastic vessel in the cecum (Fig. 8). Colonoscopy confirmed the presence of the above.

The patient was treated with digoxin, lasix and packed cells in preparation for surgery. A right hemicolectomy was performed without incident. There was no further gastrointestinal bleeding during an eight-month follow-up period.

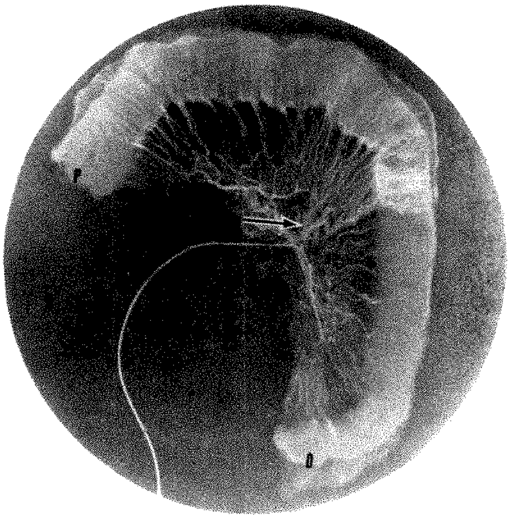

Fig. 7—Case 4, the resected jejunum was injected with a gelatin mixture showing an abnormal blush of the bowel and a large vein draining the malformation.

## COMMENT

The controversy in medical opinion as to whether patients with aortic stenosis have an increased tendency to bleed from the gastrointestinal tract was first noted in 1958. Two letters in the *New England Journal of Medicine,* one by Heyde[1] and one by Schwartz,[2] suggested that there was clinical association between gastrointestinal bleeding and aortic stenosis. Although they were unable to identify any specific lesion to explain the source of bleeding. Williams,[3] in 1961, reviewed the experience at Massachusetts General Hospital, after seeing four patients with massive unexplained gastrointestinal bleeding who also had aortic stenosis. In their study of 1,443 patients with gastrointestinal bleeding, the source of the bleeding was identified in 93.5% of the cases. Among 122 patients in whom the origin of the bleeding could not be discovered, 25% had aortic

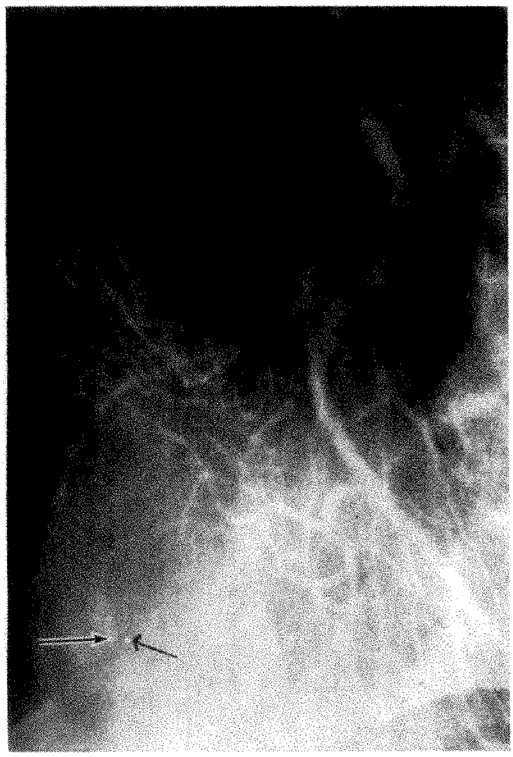

Fig. 8–Case 5, superior mesenteric arteriography demonstrates the presence of a vascular dysplastic vessel in the cecum.

stenosis. In 1965, Trowbridge[4] reported four patients with aortic stenosis and gastrointestinal bleeding. Two of this group had no demonstrable lesion to explain the bleeding. McNamara and Austin[5] in 1968 reviewed a series of patients admitted for aortic or mitral valve replacement who had a history of gastrointestinal bleeding. A higher incidence of gastrointestinal bleeding was found in the aortic group (12%) as opposed to the mitral group (4%). In 20% of the aortic group a source of bleeding was never identified. This raised the suspicion of an obscure lesion such as a vascular malformation.

Boss and Rosenbaum in 1971 reported a patient with aortic stenosis who had recurrent gastrointestinal bleeding of obscure etiology in whom at autopsy, the origin of the bleeding was found in the right colon.[6] Microscopic sections of the colonic tissue showed distention of the mucosal and submucosal veins and focal perivascular extravasation of blood. No evidence of vasculitis could be found.

In 1974 Galloway, et al,[7] reported three patients with aortic stenosis in whom vascular malformation of the right colon demonstrated by visceral arteriography was found to be the cause of recurrent gastrointestinal bleeding.

The diagnosis of aortic stenosis in such patients is usually made on clinical grounds. Table I summarizes the findings in the group described in this report. Patients in most groups present with a characteristic systolic ejection murmur at the aortic area radiating to the neck; a thrill which may or may not be felt. The second aortic sound is often diminished and a plusus parvus and tardus is often present. An x-ray of the chest usually demonstrates an enlargement of the left ventricle with poststenotic dilatation of the aorta and calcification of the aortic valves in the lateral views.

Many patients with this condition have a history of repeated bouts of often massive intestinal hemmorrhage for as long as 20 years. In most instances it occurs in people over 50 years of age and often in much older ones. It is not uncommon to find octagenarians with this syndrome.

In patients with gastrointestinal bleeding secondary to an arteriovenous malformation of the cecum or ascending colon, angiography is the most useful radiographic procedure. Unfortunately, until the introduction of selective mesenteric angiography by Odman[8] in 1958 and popularized by Baum and co-workers[9] in 1965, the exact nature of the lesion could not be iden-

TABLE 1

| Case | Sex | Age | Murmur | LVH | Hct. | Hgb. | Guaiac stools | Upper and lower barium | Angiography | Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | F | 65 | IV/VI ejection systolic | + | 25% | 5 gm. | + | 0 | Angiodysplasias in cecum and ascending colon | Hemicolectomy |
| 2. | F | 65 | IV/VI aortic systolic | + | 26% | 6 gm. | + | 0 | " " | " |
| 3. | F | 79 | Aortic systolic | + | 27% | 7 gm. | + | 0 | " " | " |
| 4. | M | 74 | IV/VI basal ejection systolic | + | 22% | 6 gm. | + | 0 | Vascular malformation in jejunum | Jejunal resection |
| 5. | M | 90 | IV/VI aortic systolic | + | 30% | 8 gm. | + | 0 | Angiodysplasia in cecum | Hemicolectomy |

tified and was often overlooked. Barium enemas are consistently negative because these lesions create no mass effect. Selective catherization of the superior mesenteric artery is necessary to demonstrate the malformation. The angiographic hallmark of the lesion is an early draining vein, i.e. a vein that fills during the arterial phase of the study. This vein is also denser than the rest of the veins draining the bowel. While A-V shunting may be the only positive finding, the malformation itself may be seen as a series of dilated and tortuous arterial branches.

Colonoscopy at times may be helpful in detecting the presence of angiodysplasias as shown in Case 5 but as a rule it is not very productive. The colonoscopic appearance of the mucosal component of the lesion when seen is usually that of a cherry red dilated array of vessels varying in size from 1-10 mm. Occasionally, as in our patient, a very large blue submucosal vein may be seen draining the lesion. Inasmuch as 60% of such lesions have no mucosal component, colonoscopy is often not helpful.

The true frequency of angiodysplasias of the intestinal tract is unknown. Boley, et al[10] found that in a group of patients 60 years of age with no history of bleeding, mucosal ectasias were present in 27% and submucosal ectasias in 53%. Interestingly, Boley noted that five of their 23 patients with proven ectasias had aortic stenosis and 20-25% of previously reported patients with ectasia also had aortic stenosis.

The etiology of the association of aortic stenosis and angiodysplasia is unknown and purely speculative. There is some controversy as to whether the vascular malformation seen in aortic stenosis is congenital or acquired. Inasmuch as the cause of the lesion of aortic stenosis in the elderly is more often congenital, one might accept the congenital theory. In opposition is the fact that gastrointestinal bleeding has not been noted to occur in young patients with aortic stenosis. Boley, et al[10] believe that vascular ectasias are common degenerative lesions of aging. They do not believe that the low perfusion pressure and low pulse pressure produced by aortic stenosis contribute to the development of vascular ectasias as formerly postulated by others. They believe that the low perfusion pressure may increase the chance of bleeding in persons with ectasias. Atherosclerosis with peripheral ischemia and subsequent arteriovenous shunting, also has been considered, since all the patients are in the geriatric age group. Superior mesenteric arteriograms in such patients, however, failed to demonstrate the lesion.

In the series reported by Galloway, et al,[7] one of their patients had hypertrophic subaortic stenosis thus negating the concept that this lesion is solely due to aortic stenosis. As previously mentioned, vascular malformations of this type are not limited to patients with aortic stenosis and indeed may occur in patients without an underlying cardiac disorder. In William's series[3] a high percentage of positive serologic test was noted among the idiopathic bleeders with aortic stenosis raising the possibility of syphilitic endarteritis in the mesenteric vascular bed. None of the patients in the author's series, however, reported such a coincidence.

It is apparent that there is much to be learned about the unknown relation between aortic stenosis in the elderly and angiodysplasias of the gastrointestinal tract causing recurrent bleeding. It is interesting to note that in patients with aortic stenosis who had lower gasrointestinal bleeding and who underwent surgery for correction of the aortic stenosis, the bleeding did not recur for several years postsurgery. The latter observation suggests that correction of the valvular disease influenced the gastrointestinal bleeling.

As previously mentioned the bleeding site in patients with aortic stenosis is often in the right colon but it may occur in other parts of the gastrointestinal tract. The routine x-ray examinations of the gastrointestinal tract often do not detect the hemorrhage source. Selective mesenteric angiography,[8] however, and at times magnification of arteriography[10] are the best procedures which will localize the lesion. Occasionally colonoscopy may be of value in the condition but to date it has not been proven to be uniformly successful. Once the diagnosis is established surgery is mandatory. An awareness of the clinical entity and its diagnosis utilizing selective mesenteric angiography may prove to be lifesaving in recurrent lower gastrointestinal bleeding in the elderly.

## ACKNOWLEDGMENT

Our thanks to the Department of Medicine at Booth Memorial Medical Center for permission to report Cases 2 and 3.

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# Percutaneous Transhepatic Cholangiography with the Chiba Needle

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Ninety patients with suspected pathology of the biliary tract were submitted to percutaneous transhepatic cholangiography. Forty-two of 43 dilated biliary tracts and 32 of 47 without dilatation were successfully entered. Except for fever following the procedure in two patients, there was no major complication. This technic was of prime importance in the management of patients with suspected pathology of the biliary tract.

## INTRODUCTION

The percutaneous transhepatic cholangiography by the conventional method has generally been reserved for jaundice of uncertain etiology.[1-6] Although the success rate was high when the biliary tract was dilated, ranging from 79-95%,[3] it was rather low in the absence of dilatation, ranging from 10-47%.[1, 4-6] This is insufficient since the dilatation may be minimal or even absent in the presence of an obstruction.[5, 7] Furthermore, because of possible complication, the procedure had to be followed by immediate laparotomy when an obstruction was disclosed.[1-6]

Since a refined method using a thin and flexible needle has been developed by Ohto[8] and Tsuchiya[9] and was popularized by Okuda,[10] several reports have claimed its efficacy and safety.[11-13] Immediate laparotomy was judged unnecessary in most cases[11] and the procedure could also be extended to suspected pathology of the biliary tract without jaundice.[10, 14]

The results of our first 90 cases of percutaneous transhepatic cholangiography with the "skinny Chiba needle" are reported here.

## MATERIALS AND METHODS

From 1975-1977, 90 patients, aged 20-79 years, with jaundice of uncertain etiology, pancreatitis or abdominal pain of suspected biliary origin were subjected to percutaneous transhepatic cholangiography when other methods such as intravenous cholangiography and endoscopic retrograde cholangiography failed or were contraindicated.

Sepsis, profound anemia, ascites, iodide sensitivity, prothrombin time of more than three seconds over control platelet count of less than 75 × $10^3$ cu. mm. and lack of co-operation were considered as contraindications.

Prophylactic antibiotherapy was started two days before the procedure and pursued at least for five days in the presence of jaundice or a history suggesting previous

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TABLE I

| Diagnosis | Biliary tract entered | Biliary tract not entered |
|---|---|---|
| Choledocholithiasis | 14 | 1 |
| Pancreatitis | 6 | 0 |
| Common hepatic duct ligation | 1 | 0 |
| Postoperative choledochus stricture | 1 | 0 |
| Pancreatic carcinoma | 8 | 0 |
| Bile duct carcinoma | 4 | 0 |
| Metastatic carcinoma of other sites | 6 | 0 |
| Unknown | 2 | 0 |
| Total | 42 | 1 |

TABLE II

| Diagnostic | Biliary tract entered | Biliary tract not entered |
|---|---|---|
| Choledocholithiasis | 3 | 1 |
| Cholecystitis | 1 | 3 |
| Pancreatitis | 15 | 4 |
| Cirrhosis | | |
| Primary biliary | 0 | 2 |
| Alcoholic | 1 | 1 |
| Cryptogenic | 1 | 0 |
| Hepatitis | | |
| Alcoholic | 2 | 1 |
| Viral | 1 | 2 |
| Pancreas carcinoma | 2 | 0 |
| Functional pain | 3 | 1 |
| Unknown | 3 | 0 |
| Total | 32 | 15 |

ascending cholangitis. Vitamin K was given as needed. Meperidine, 50 mg. and Promethazine, 25 mg. were given intramuscularly as premedication in some patients. Meglumine diatrizoate 60% (Renografin 60[*]) was used as contrast material. The needle developed at the University of Chiba, Japan, was used in all cases. This is a flexible 15 cm. long, 22 gauge needle, 0.7 mm. in outer and 0.5 mm. in inner diameter with a 30° bevel.

The right flank of the patient lying supine on the radiology table with the right arm under his head was disinfected and draped to provide a surgical working area. A metallic marker was fixed over the xyphoid process. Local anesthesia was achieved with 2% lidocaine chlorhydrate. Under fluoroscopy the needle entered the liver during apnea at the level of the 7th or 8th intercostal space in the mid axillary line and was parallel to the radiology table toward the metallic marker as far as 1 cm. from the right border of the vertebral column. The mandrel was removed and a 30 ml. glass syringe containing the contrast material was connected to the needle through a polyethylene tube. The needle was then slowly withdrawn while gently injecting the least amount of contrast material possible. Intraparenchymal injection resulted in a permanent woolly spot sometimes accompanied by an epigastric discomfort, intravascular injection by a rapid wash-out while intraductal injection showed a slow and dense flow to the hepatic bilum. If no bile duct was entered, a new course was carried out by the same entry but the needle was directed a little more cephalad and anteriorly. A maximum of six tracks was arbitrarily permitted. The amount of contrast material injected depended on the degree of dilatation of the biliary tract and varied between 10 and 60 ml. in general. Films were taken at different inci-

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[*] E. R. Squibb & Sons, Ltd. Montreal.

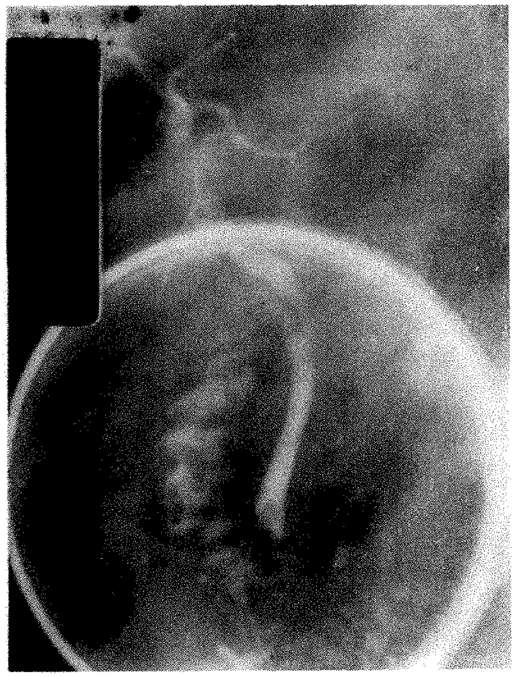

Fig. 1—Percutaneous transhepatic cholangiography of Case 1 showing the choledocholithiasis with absence of any dilatation of the biliary tract.

dences. When an obstruction was disclosed as much bile as possible was withdrawn at the end of the procedure through the needle by free flow or by aspiration. A specimen of bile was sometimes submitted to microbiologic studies. After the needle was removed, close surveillance was exercised for at least six hours to detect any sign of complication.

Dilatation was considered with a diameter over 6 mm. for the right hepatic duct, over 7 mm. for the left hepatic duct, over 8 mm. for the common duct and over 10 mm. for the choledochus.[7, 10] In all cases where the biliary tract could not be successfully opacified, other procedures such as endoscopic retrograde cholangiography, peroperative cholangiography or intravenous cholangiography were used. In all but five cases (two with dilated and three without dilated ducts) was the ultimate diagnosis determined by laparotomy, autopsy, liver biopsy, biology and/or evolution.

## RESULTS

The over all success rate was 82.2%; 74 of 90 biliary tracts were entered. Forty-two of 43 dilated tracts (success rate of 97.6%) and 32 of 47 undilated tracts (success rate of 68%) were entered. The encountered lesions are reported in Tables I and II.

The correlation between the radiologic diagnosis and the ultimate diagnosis was high. In 60 out of 69 cases the radiologic diagnosis was in agreement with the final diagnosis proven by other means. In five further patients, the procedure could not distinguish between a benign or malignant obstruction and in four more cases the radiologic diagnosis was wrong.

There was no major complication. In no case was there any evidence of significant bile leakage or hemorrhage on a clinical, laboratory and/or surgical basis. In two cases (2.2%) the procedure was followed by fever of 39° C accompanied in one case by chills that lasted only a few hours and had no apparent influence on the clinical course. Pain was quite frequent although in general of moderate or light severity and was recorded in 23 cases (25.5%). In two cases, however, extrahepatic injection of contrast medium produced severe pain so that the procedure had to be interrupted. Blood pressure drop exceeding 20 mm Hg. occurred in 17 cases (18.8%) and was often accompanied by bradycardia. In no case could this be correlated with a drop of hemoglobin and no patient had to be operated because of the procedure.

## CASE REPORT

*Case 1:*—M. T. is a 52-year old man who underwent a cholecystectomy in 1973

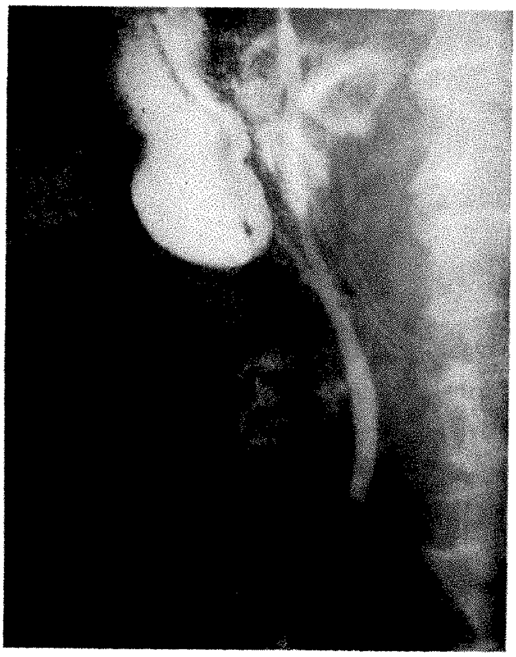

Fig. 2—Percutaneous transhepatic cholangiography of Case 2 showing a slight deformation of the lower end of the choledochus without dilatation.

in another hospital for a symptomatic but uncomplicated cholelithiasis.

A few months after operation he started to complain of the same type of pain. He was seen in our hospital in 1976 when physical examination was normal. The laboratory results were also normal: SGOT, 27 I.U./ml. (normal: 10-90); SGPT, 50 I.U./ml. (normal: 20-90); bilirubin: direct, 0.2 mg.%, indirect, 0.35 mg.%; alkaline phosphatase, 81 I.U./ml. (normal: 20-85); leucine aminopeptidase, 155 I.U./ml. (normal: 75-230); prothrombin time, 100% of control; amylase, 52 I.U./ml. (normal: 80-150), blood cell count normal.

Because of a history of bouts of abdominal pain, an I.V. cholangiogram was performed which was read as within normal limits. An endoscopic retrograde cholangiography was unsuccessful. A percutaneous transhepatic cholangiography disclosed a stone in the lower choledochus (Fig. 1). A choledochotomy was performed and a 5 mm. diameter stone extracted.

*Case 2*:—This is a 72-year old man with a three week history of poor appetite and a loss of 6.75 kg., epigastric pain, nausea and vomiting; he also complained of a pain in the right calf. On physical examination, there were signs of peritoneal irritation; the liver and spleen were not palpable. Right calf tenderness and ankle edema on both sides were noted.

Laboratory results were: total bilirubin, 0.95 mg.%; direct bilirubin, 0.2 mg.%; SGOT, 219 I.U./ml.; SGPT, 172 I.U./ml.; alkaline phosphatase, 347 I.U./ml.; leucine aminopeptidase, 170 I.U./ml.; prothrombin time, 1.5 sec. over control; amylase, 480 I.U./ml. (normal: 80-150); lipase, 1.0 I.U./ml. (normal: 0-0.6); leucocyte count 17,400/cu. mm.; neutrophils, 81%; eosinophils, 1%; basophils, 5%; lymphocytes, 15%; monocytes, 3%.

The upper gastrointestinal series and barium enema were normal; the cholecystography showed a normal gallbladder. There was a decrease in the uptake of the radiocolloid in the right lobe of the liver and thrombosis in the right leg with pulmonary embolism was suggested on the scan.

As jaundice was rapidly progressing, a percutaneous transhepatic cholangiography with the Chiba needle was performed (Fig. 2). At laparotomy, cancer of the head of the pancreas was confirmed with liver metastasis. The patient died a few days later and on autopsy, pulmonary metastasis and multiple embolism were also seen.

## COMMENT

In this series the biliary tract was successfully entered in 97.6% of cases when it was dilated and in 68% of cases when it was not. These results are comparable with previously reported series.[10, 11, 13, 14] This technic was of great help in detecting the nature, the site and the extent of the obstruction allowing an early and correct therapeutic approach. The exclusion of an obstructive lesion was of prime importance in the further management of cirrhosis, hepatitis and pancreatitis.

In the majority of the cases, there seems to be a good correlation between radiologic and pathologic findings; however the x-rays were not read on a double-blind basis.

Although it has been stressed that failure to enter a biliary tract virtually rules out any dilatation,[11-13] caution should be exercised since in this series, one of 43 dilated biliary trees could not be entered. Also, more significantly, there was no dilatation in two cases of carcinoma of the pancreas involving the choledochus and in four cases of choledocholithiasis. It is therefore necessary to use other technics to visualize the biliary tract in all cases where the percutaneous transhepatic cholangiography failed. In this respect the endoscopic retrograde cholangiography is quite complementary.[14] Nevertheless this procedure requires special training and expensive equipment while its success and complication rates are comparable.[15]

No major complication developed in this series. Yet two patients had episodes of fever that lasted only a few hours probably because appropriate antibiotherapy had already been started. In the reported series using the Chiba needle, the complication rates ranged from 3.1-7.96%[10, 11, 12] and there was no death. The complication rate was similar to that observed with the conventional method, that is 5% of 1,629 reported cases.[4] But as already suggested[14] these two groups of reports are difficult to compare since laparotomy was in general postponed with the newer method allowing complications to develop. Since the few reported complications supervened principally in cases of dilated bile ducts the old principle of early laparotomy should an obstruction be disclosed cannot be ignored even if there was no major complication in this series. Aspiration of bile in cases of obstruction[10-14] should minimize the risk of complication but in our hands this could not frequently be done, probably because of the high resistance to bile flow through the very narrow needle.[14]

Percutaneous transhepatic cholangiography with the Chiba needle is a valuable technic that can be done without special training and at no expense. It permits an early diagnosis in difficult cases of jaundice and can be extended to any suspected pathology of the biliary tract and to the direct measurement of portal and hepatic vein pressures.[16]

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# Exocrine Pancreatic Function Test by a Synthetic Peptide

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A new synthetic substance, N-Benzoyl-L-tyrosyl-p-aminobenzoic acid, is specially cleaved by pancreatic chymotrypsin after oral administration and the released p-aminobenzoic acid (P.A.B.A.) is absorbed and excreted in the urine. The P.A.B.A. recovery in the urine was examined to evaluate its diagnostic value as an exocrine pancreatic function test. The data permit the following conclusions: 1. There is a significant correlation between this test and maximal bicarbonate concentration, amylase output and volume of P.Z./C.C.K. secretin test. 2. More than one-half to two-thirds proximal or one-third distal of the pancreas must be removed before one can expect an abnormal result in this test. 3. This is a simple and useful test to detect exocrine pancreatic insufficiency of more than moderate degree but normal results may be obtained in minimal to mild exocrine pancreatic insufficiency. Only six of 11 cases (54.5%) with one abnormal factor of P-S test showed decreased P.A.B.A. recovery, whereas 22 of 23 cases (95.7%) with two or three abnormal factors of P-S test showed decreased or borderline P.A.B.A. recovery.

Secretin-C.C.K./P.Z. test or P.Z./C.C.K.-secretin test (P-S test) has widely been used as the most reliable method for evaluation of exocrine pancreatic function. The procedure, however, is time-consuming and unacceptable to some patients. In addition, only a limited number of cases can be examined in a day even in large hospitals with fine facilities. In 1972, Imondi, et al[1, 2] introduced a new substance N-benzoyl-L-tyrosyl-p-aminobenzoic acid (Bz-ty-P.A.B.A.) which is specifically cleaved by chymotrypsin liberating Bz-ty and P.A.B.A. Their data suggested that the measurement of P.A.B.A. and derivatives recovered in the urine following oral administration of the substance would be useful as a simple and practical exocrine pancreatic function test. This test, which will be designated as PFT in the following discussion, has been evaluated by several investigators[3-6] who reported that PFT is significantly decreased in well established cases of chronic pancreatitis and in cancer of the pancreas and that there is a statistically significant correlation between PFT

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TABLE I

GRADING OF ABNORMALITY IN P-S TEST

| P-S test grading | MBC (mEq./l.) | Amylase output (Caraway unit) | Volume (ml.) |
|---|---|---|---|
| Minimal | | A little below the borderline | |
| Mild | $> 60$ | $> 4.0. \times 10^4$ | $> 60$ |
| Moderate | 40-60 | $4.0 \times 10$-$2.5 \times 10^4$ | 40-60 |
| Marked | $< 40$ | $< 2.5 \times 10^4$ | $< 40$ |

and enzyme secretion of the pancreas. Clarification remained to be determined, however, as to how the PFT test compared to the ordinary P-S test or Lundth test in disclosing minimal to moderate degrees of pancreatic disease. Also to be determined was whether the test is specific in evaluating the exocrine pancreatic function. This report is concerned with clinical studies using PFT to diagnose pancreatic disease.

## MATERIALS

The study group consisted of 29 healthy controls, 11 cases of possible chronic pancreatitis, 17 cases of chronic pancreatitis without calcification, 22 cases of chronic pancreatitis with calcification, eight cases of acute pancreatitis in remission stage, 13 cases of pancreas cancer, 11 cases following partial pancreatectomy. The 11 cases of suspected chronic pancreatitis were patients with clinical history and findings suggestive of chronic relapsing pancreatitis as well as hyperamylasuria but with no abnormality of P-S test. Chronic pancreatitis was diagnosed on the basis of clinical history and findings suggestive of chronic relapsing pancreatitis plus an abnormal P-S test. In all 22 cases of pancreatolithiasis, calculi were revealed in the main pancreatic duct (MPD) and its branches on endoscopic retrograde pancreatography (ERP). Cancer of the pancreas was confirmed by histological examination. Partial pancreatectomy had been performed for cancer of the pancreas in four cases, ampullary cancer in one case, chronic pancreatitis in three cases, stomach cancer in two cases and perforated ulcer in one case, respectively.

## METHODS

Five tenths of a gram of Bz-ty-P.A.B.A. was administered orally with 250 ml. of water in early morning after overnight fasting. The amount of P.A.B.A. and its derivatives in the six-hour urine was measured by the method of Bratton and Marshall as modified by Smith, et al. Results were conveyed as percentage of P.A.B.A. and derivatives recovered in the urine as compared with the applied dose. All drugs were discontinued at least 24 hours before the investigation. During the six-hour urine collection, nothing per mouth was allowed except for water. Bz-ty-P.A.B.A. was supplied by Eisai Co. Ltd., Japan. P-S test was performed, using the Dreiling double-lumen tube. Pancreozymin 1 Boot unit/kg. was intravenously injected for stimulation of pancreatic secretion.

Following 20-minute collection of the duodenal content, secretin 1 Boot unit/kg. was injected intravenously to obtain pancreatic juice in 10-minute fractions for 60 minutes. The specimens were analyzed for volume, bicarbonate concentration, amylase activity, pH and bile pigment. Results were

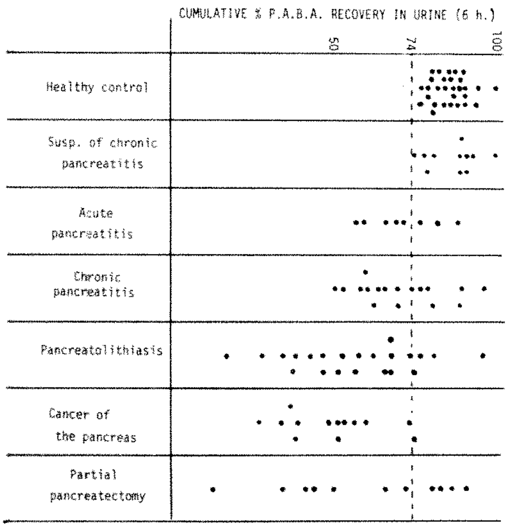

Fig. 1—Cumulative six-hour P.A.B.A. recovery in the seven groups of subjects.

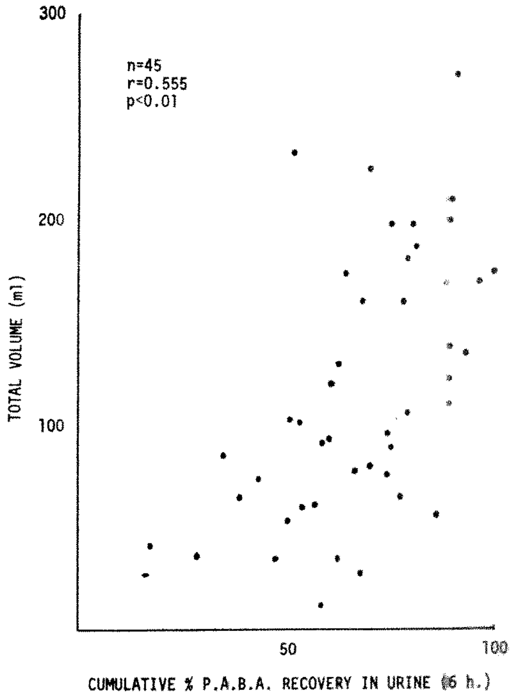

Fig. 2—Correlation of P.A.B.A. recovery with volume on P-S test.

evaluated on the basis of three factors consisting of volume, maximal bicarbonate concentration (MBC) and amylase output. Grading of abnormality was made as described in Table I. ERP was performed with Olympus JF-B2 as described previously.[7]

## Results

*Healthy controls (Fig. 1):*—PFT in 29 healthy controls was 85.6 ± 10.9 (mean ± 2SD).

*Suspicion of chronic pancreatitis (Fig. 1):*—Ten of 11 cases showed normal PFT and one case showed borderline PFT. PFT in this group was 86.9 ± 7.5 (mean ± SD) and no significant difference was found between this group and healthy controls.

*Chronic pancreatitis without calcification (Fig. 1):*—PFT in this group was 70.63 ± 13.22 (mean ± SD) and a significant difference ($P < 0.01$) was found between this group and healthy controls. Five of 17 cases (29.4%) showed normal PFT and two cases showed borderline PFT. Five cases with normal PFT showed a minimal decrease of volume in two cases, a minimal decrease of amylase output in one case, a minimal decrease of MBC in one case and a mild decrease of MBC in one case, respectively, on repeat P-S test. Two cases with borderline PFT showed a minimal decrease of amylase output and a mild decrease of volume in one case and a mild decrease of MBC, volume and amylase output in one case, respectively, on repeat P-S test. Ten cases with abnormal PFT showed a mild decrease of volume and borderline amylase output in two cases, more than moderate decrease in MBC or amylase output in three cases and more than moderate decrease of MBC and amylase output in two cases, a mild decrease of volume and MBC in one case, a mild decrease of amylase output and a minimal decrease of MBC in one case and a mild

TABLE II

CASES FOLLOWING PARTIAL PANCREATECTOMY

| Patient | Age | Diagnosis | Extent of pancreatectomy | PFT |
|---|---|---|---|---|
| H.K. | 46 | Chronic pancreatitis | Proximal 2/5 of pancreas | 86.4 |
| T.M. | 54 | Pancreas cancer | Distal 1/2 of pancreas | 49.9 |
| K.F. | 32 | Perforated ulcer | Proximal 1/5 of pancreas | 72.4 |
| M.N. | 77 | Pancreas cancer | Distal 1/2 of pancreas | 34.3 |
| C.Y. | 69 | Ampullary cancer | Distal 1/3 of pancreas | 80.4 |
| R.N. | 66 | Stomach cancer | Proximal 1/2 of pancreas | 44.1 |
| Y.Y | 51 | Stomach cancer | Proximal 2/5 of pancreas | 91.0 |
| T.T. | 65 | Pancreas cancer | Distal 1/2 of pancreas | 12.8 |
| T.N. | 58 | Pancreatolithiasis | Proximal 1/3 and distal 1/4 | 41.4 |
| K.D. | 61 | Chronic pancreatitis | Proximal 1/3 of pancreas | 65.9 |
| Y.Y. | 50 | Pancreas cancer | Proximal 1/2 of pancreas | 83.1 |

decrease of amylase output and a moderate decrease of MBC in one case, respectively, on repeat P-S test.

*Chronic pancreatitis with calcification (Fig. 1)*:—PFT in this group was 56.67 ± 19.1 (mean ± SD) and a significant difference ($P < 0.01$) was found between this group and healthy controls. Eighteen cases showed extensive and diffuse distribution of calculi in the pancreatic ducts on ERP. Sixteen of the 18 cases showed abnormal PFT. In these 16 cases, ERP revealed extensive changes of the pancreatic duct system (PDS), consisting of dilatation, stenosis, obstruction and rigidity. The remaining two cases had borderline values, 74.7% and 77.1%. In these two cases, diffuse dilatation and irregularity of PDS was the only abnormality revealed on ERP. Among the remaining four cases, calculi were localized in the body of the pancreas in one case and in the tail in three other cases. PFT was within normal limits in two of the four cases, 95.9% and 81.2% respectively. In these two cases, dilatation of PDS localized in the body and tail of the pancreas was the only abnormal finding revealed on ERP. The remaining two cases showed borderline to abnormal PFT, 73.7% and 67.8% respectively. In these two cases, calculi were localized but numerous and ERP revealed extensive and multiple changes of PDS, including dilatation and irregularity. P-S test was evaluable in 14 cases. Two cases with borderline PFT showed a mild decrease of amylase output and volume in one and a marked decrease of MBC and a mild decrease of volume in another, respectively. Among 12 cases with abnormal PFT, more than moderate decreases of all three factors were noted in four cases, more than moderate decrease of amylase output and MBC in two cases, more than moderate decrease of volume and amylase output in two cases, more than moderate decrease of volume and MBC and a mild decrease of amylase output in one case, a marked decrease of MBC and a mild decrease of amylase output in one case, a moderate decrease of MBC in one case, and a mild decrease of all three factors in one case, respectively, on repeat P-S test.

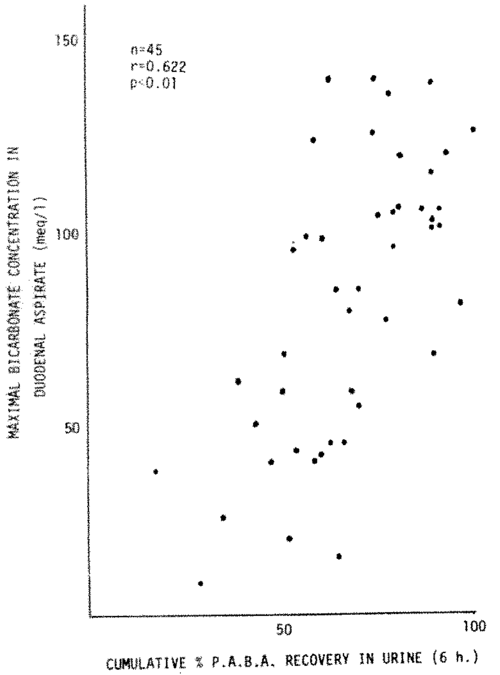

Fig. 3—Correlation of P.A.B.A. recovery with maximal bicarbonate concentration on P-S test.

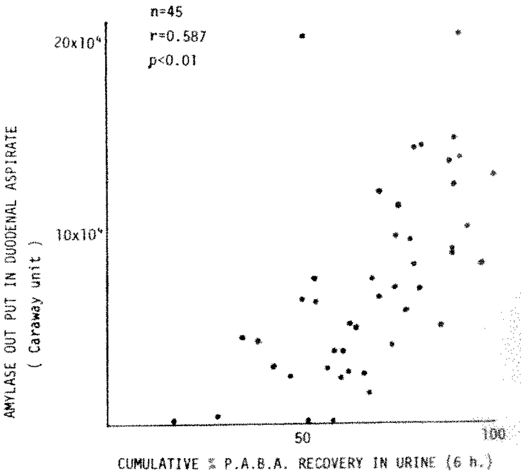

Fig. 4—Correlation of P.A.B.A. recovery with amylase output on P-S test.

*Carcinoma of the pancreas (Fig. 1):*—PFT in this group was 49.62 ± 14.3 (mean ± SD) and a significant difference was found between this group and healthy controls ($P < 0.01$). All of 13 cases had jaundice at the time of examination. Eleven of the 13 cases showed abnormal PFT. In all of these 11 cases, ERP revealed complete obstruction of MPD within 6 cm. from the distal end (Vaterian papilla). In one case with borderline PFT, in contrast, ERP revealed moderate stenosis of the MPD in the head of the pancreas and dilatation of PDS in the body and tail but outflow of contrast material was complete only with delay of moderate degree. In another case with borderline PFT, ERP revealed only abnormality of branches in the head without stenosis of MPD. P-S test was available in two cases with abnormal PFT and revealed a moderate decrease of volume and amylase output in one and a moderate decrease of volume and MBC in another.

*Cases that had undergone partial pancreatectomy (Fig. 1 and Table II):*—PFT in this group was 60.16 ± 25.28 (mean ± SD) and a significant difference was noted between this group and healthy controls ($P < 0.01$). Four of 11 cases showed normal PFT. Among these three had undergone resection of proximal two-fifths to one-half (tail and part of the body) of the pancreas. P-S test in one of the three patients with normal PFT showed a moderate decrease of volume and a minimal decrease of amylase output. The fourth case with normal PFT had had distal one-third of the pancreas (head) removed for the ampullary carcinoma.

*Postacute pancreatitis cases (Fig. 1):*—Five of eight cases showed abnormal PFT. In four of these five cases, examination was performed about a month following the recovery from the acute attack. In the remaining one case, PFT was still abnormal two years after the acute attack, at which time hemorrhagic and necrotic pancreatitis was observed laparoscopically. In three cases

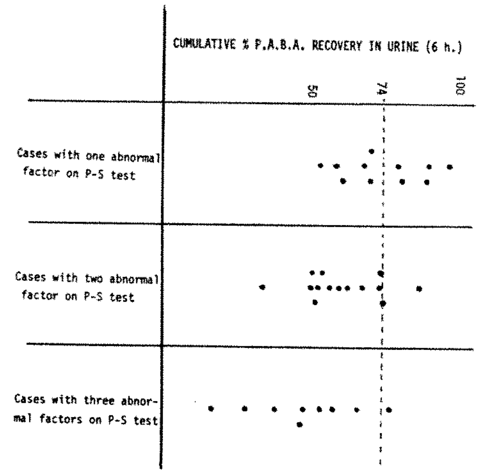

Fig. 5—Comparison of PFT and P-S test.

with normal PFT, more than four months had elapsed after the acute attack.

*Comparative studies of PFT and P-S test (Figs. 2, 3, 4):*—PFT was compared with each of the three diagnostic parameters (MBC, volume and amylase output) of the P-S test in 45 cases, consisting of 11 cases of suspected chronic pancreatitis, 17 cases of chronic pancreatitis, 14 cases of pancreatolithiasis, two cases of pancreas cancer and one case of postpancreatectomy.

The correlation coefficient was 0.587 for amylase output, 0.622 for MBC and 0.555 for volume. Thus, statistically significant correlation was found between PFT and each factor of P-S test ($P < 0.01$). PFT was compared in cases with one, two, and three abnormal parameters of P-S test (Fig. 5). Only six of 11 cases (54.5%) with one abnormal factor showed definite abnormal or borderline PFT (Fig. 5). PFT was 74 ± 14.03 (mean ± SD) in cases with one abnormal factor, 62 ± 13.15 in cases with two abnormal factors and 47.57 ± 18.64 in cases with three abnormal factors. There was a significant difference between the group with one abnormal factor and the group with two or three abnormal parameters ($P < 0.05$) but no significant difference was noted between the group with two abnormal factors and the group with three abnormal parameters.

## COMMENT

The present data confirm the results of other investigators[3-6] that PFT is significantly decreased in: 1. established cases of chronic pancreatitis with or without calcification; 2. in some cases of acute pancreatitis; 3. in cancer of the pancreas and 4. following pancreatectomy. Moreover, there is a significant correlation between PFT and amylase output, MBC and volume. Thus, it can safely be said that PFT is a simple, practical and reliable test for the evaluation of exocrine pancreatic function. It is of note, however, that five cases (29.4%) of chronic pancreatitis without calcification, two cases (14.3%) of chronic pancreatitis with calcification and four cases (36.4%) following pancreatectomy revealed normal PFT. The results of PFT in chronic pancreatitis with calcification indicate that only borderline PFT may be obtained when diffuse dilation and irregularity of PDS are the only abnormal findings revealed on ERP and that normal PFT may be obtained when dilation and irregularity of PDS are localized in the body and tail.

The results of the PFT test in cancer of the pancreas indicate that the MPD must be completely obstructed within less than 6 cm. (about distal one-third of the total length of MPD) from the Vaterian papilla before abnormal PFT can be obtained. The results of PFT obtained in cases following partial pancreatectomy indicate that more than the proximal one-half (tail and a part of body) of the pancreas or more than the distal one-third (head) of the pancreas must be removed before abnormal PFT can be obtained.

TABLE III

COMPARATIVE STUDY OF PFT AND P-S TEST

| PFT<br>PFT and P-S test | Normal | Borderline | Abnormal |
|---|---|---|---|
| More than moderate decrease of amylase output | | | 13 |
| More than moderate decrease of MBC | | 1 | 15 |
| Mild decrease of any two of three factors, amylase output, MBC, and volume | | 2 | 3 |
| Borderline to minimal decrease of amylase output with mild decrease of volume | 1 | 1 | 2 |
| Minimal decrease of amylase output | 1 | | |
| Minimal to mild decrease of MBC | 2 | | |
| Minimal decrease of volume | 2 | | |

A comparative study of PFT and P-S test reveal that 45.5% of cases with an abnormality of only one factor on P-S test may show abnormal PFT, whereas cases with an abnormality in more than two factors on P-S test almost always show borderline or abnormal PFT.

A detailed comparative study of PFT and the results of P-S test are summarized in Table III and allows the following conclusions; 1. More than moderate decrease of amylase output results in abnormal PFT. 2. More than moderate decrease of MBC results in abnormal PFT in most cases but borderline PFT may be obtained in occasional cases. 3. Mild decrease of any two of three factors (amylase output, MBC and volume) results in abnormal or borderline PFT. 4. Mild decrease of MBC alone is likely to result in normal PFT. It remains to be determined whether abnormal PFT will be observed with mild decrease of amylase output alone. 5. Minimal decrease of amylase output with mild decrease of volume may result in normal, borderline or abnormal PFT according to circumstances. 6. Minimal decrease of any one factor is likely to result in normal PFT.

## SUMMARY

The data indicate that abnormal PFT can hardly be expected in cases with lesions of minimal degree or in cases with localized lesions of the pancreas unless the MPD is completely obstructed in the head or distal part of the body of the pancreas by the lesion. It is also demonstrated that PFT is likely to be somewhat inferior to P-S test in detecting a minimal to mild exocrine pancreatic insufficiency. Accordingly, normal PFT does not necessarily rule out the presence of pancreatic lesions and borderline PFT should lead to a further extensive examination of the pancreas. In contrast, abnormal PFT almost always points to the presence of pancreatic lesions if the procedure is correctly performed.

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# Effect of Gastrin on the Exocrine Pancreas

## A REVIEW

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Studies in animals demonstrate a gastric hormonal phase of pancreatic exocrine secretion. Endogenous or exogenous gastrin causes a marked elevation in the pancreatic enzymes and a lesser increase in the pancreatic volume and bicarbonate. It is possible that these "gastrin" effects may be the basis of a "cephalic" phase of pancreatic secretion. These observations have been only partially confirmed in human subjects with and without the Zollinger-Ellison syndrome. The physiologic importance of these ecbolic actions as well as a possible trophic effect remains to be elucidated.

### INTRODUCTION

Problems in the management of acute pancreatitis have been of long and pressing concern to the clinical surgeon, as well as the clinical investigator. The cornerstone of therapy for acute pancreatitis for many years revolved around maneuvers that would impede stimulation of pancreatic exocrine function. To this latter end, nasogastric suction was employed in the belief that it would prevent acidification of the duodenum with its resultant release of pancreatic ecbolic hormones. As an extension of this philosophy, the surgical procedure of gastrojejunostomy enjoyed a brief period of acceptance in the belief it would selectively de-acidify the proximal small intestine where the pancreatic activating enzymes, cholecystokinin and secretin were manufactured. Antacids were sometimes employed for the same reasons. The primary thrust in all these situations was de-acidification and little, if any attention, was paid to the resulting changes that might attend gastrin release induced by alkalinization of the stomach and duodenum. This review addresses itself specifically to interactions between gastrin and the exocrine functions of the pancreas.

### BACKGROUND

Even before Edkins[1] postulated the existence of the hormone gastrin and directed attention to its action on the stomach, Pavlov[2] had noted that sham-feeding dogs produced a small pancreatic secretory response of short duration occur-

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ring whether or not gastric juice entered the small bowel. Pavlov suggested that the response was vagally mediated. In 1924, Tonkich[3] fed dogs whose stomach was totally separated from the duodenum and observed pancreatic secretion. Tonkich proposed that this pancreatic flow was the result of a direct vagal action on the pancreas and did not consider the possibility of vagal release of a hormonal mediator from the gastric antrum. Ivy[4] in 1926, studied a canine esophagoduodenal preparation in which a pouch was constructed from the entire stomach. No increase in the volume of fluid collected from the duodenum was noted after acid or food was placed into the stomach. Ivy concluded that there was no gastric phase of pancreatic secretion. In 1931, Kogen[5] reported that in man, the sight and smell of meat would induce pancreatic secretion but this was attributed to the passage of gastric juice into the duodenum. In 1937, Crittenden and Ivy[6] fed meat broth to dogs in which the distal end of the stomach and the entire bowel up to the ileocecal valve were extirpated and observed an increased pancreatic secretion which they attributed to a direct vagal action. They may not have removed all of the gastric antrum and they could not have considered the possible vagal release of gastrin from the antrum since at that time controversy existed on whether the postulated hormone "gastrin" actually existed or whether the effects ascribed to gastric extracts were due to histamine. In 1929-1930, however, Drewyer and Ivy[7] published an interesting study in which vasodilator-free gastric extracts injected into dogs produced a slight increase in pancreatic secretion. In 1938[8] and again in 1942,[9] Komarov injected vasodilator-free pyloric extracts into cats. He reported not only increases in gastric secretion but also slight increases in pancreatic secretion. These studies[7-9] were considered strong evidence for the existence of gastrin as an entity separate from histamine. Komarov, however, did not attribute the increased pancreatic secretion to gastrin but to a contamination of "secretin" in the preparation. In 1959, Hudock and Lawrence[10] noted that fat, protein, amino acids, carbohydrates, $NaHCO_3$ or 50% ethyl alcohol placed into the stomach as an isolated antral pouch did not stimulate the pancreatic secretion of unanesthetized dogs. These results are in inexplicable disagreement with similar investigations reported at that time, e.g. that sham-feeding dogs[11] or chemical stimulation of the isolated gastric antrum[12, 13] would cause the release of "gastrin". In fact, in 1963, Passaro and Grossman[14] observed that a 1% acetylcholine or a 5% liver solution placed into an isolated pyloric pouch of a dog receiving an intravenous infusion of secretin and urecholine to induce a steady flow of pancreatic juice would augment pancreatic volume and protein concentration. Acidification of the isolated pyloric pouch inhibited this pancreatic response. The following year, Tracy and Gregory[15, 16] reported that intravenous injections of gastrin I or gastrin II into unanesthetized and anesthetized dogs caused a prompt slight rise in pancreatic volume and a more marked increase in the enzyme output.

## ANIMAL PANCREATIC EXOCRINE FLOW

Pentagastrin has been shown to increase the lipase concentration of rat pancreatic tissue slices and oxidation of acetate, octanoate and glucose in dog pancreatic tissue slices.[17] In one study in anesthetized rats, Gastrin I and Gastrin II and pentagastrin increased the pancreatic rate of flow and the rate of protein secretion.[18] In another study,[19] gastrin had no effect on pancreatic secretion and pentagastrin increased the enzyme concentration with changing flow. In conscious rats, gastrin, extracted from hog antral mucosa, was reported to increase the protein output with no alteration in the pancreatic flow.[20] No pancreatic response in the rat was observed, however, in response to sham-feeding when gastric juice was prevented from entering the small bowel.[21] In the rabbit, tetragastrin increased the pancreatic protein output in the *in vitro* and the *in vivo* preparation.[22] In anesthetized cats, whose pancreatic exocrine flow was maintained by secretin, hog antral gastrin extracts, prepared by the method of Jorpes and associates,[23] had no effect on pancreatic secretion.[24] Other investigators, however, studying anesthetized cats, whose vagi and splanchnic nerves had been cut, reported that extracts of hog gastric mucosa[25] or chemical or mechanical stimulation of the gastric antrum[26] increased the output of pancreatic enzymes[25, 26] but had little or no effect on the pancreatic flow.[25, 26] Blair and associates[27] published data which indicated that in the cat the pancreatic enzyme stimulating properties of antral mucosal extracts parallel their ability to increase gastric secretion. They concluded that a gastric phase of pancreatic secretion exists.[26]

In 1965, a series of experiments in dogs[28-31] firmly established that gastrin, in addition to its action on the stomach, had an effect on the exocrine pancreas. Intravenous or subcutaneous injection of porcine gastric extracts into dogs with chronic pancreatic fistulas resulted in a marked increase in pancreatic enzymes and lesser increase in pancreatic flow and bicarbonate.[28, 29] In dogs with chronic pancreatic fistulas and isolated denervated pouches of the gastric antrum transplanted to the abdominal wall, subcutaneous injection of Gastrin I or bathing the antral pouch with 0.5% acetylcholine increased the pancreatic flow and protein secretion.[30] In a similar experimental canine model, chemical stimulation of the gastric antra with 0.5% acetylcholine, liver extract or bactoprotone markedly increased the pancreatic protein output and only slightly elevated the pancreatic flow and bicarbonate output. Acidification of these gastric antra inhibited these pancreatic responses.[31] Others have also reported that intravenous injection of gastrin stimulated the pancreatic enzymes and volume of anesthetized dogs.[32] In 1966, Preshaw and Grossman reported that sham-feeding dogs with esophagostomies, gastric and pancreatic fistulas resulted in increased protein output from the pancreas but had no effect on the volume and bicarbonate levels. This effect was not dependent upon the passage of acid into the duodenum because the acid was drained to the outside by a gastric fistula. This pancreatic response to sham-feeding could be inhibited by acidification of the pyloric antrum.[33] The investigators did not accept this inhibition of the sham-feeding response by acidification of the antral pouch as proof that gastrin was the sole mediator, since surgical preparation of the pouch could have denervated the pancreas and thus removed neural mechanisms. In another study[34] of chronic gastric and pancreatic fistulas in dogs, one group of dogs had a selective gastric vagotomy (with the preservation of the parasympathetic innervation to the pancreas but elimination of vagal-gastrin release) and a second group had a selective extragastric vagotomy (that divided the important vagal pancreatic fibers but preserved the vagal-gastrin mechanism). Increased pancreatic enzyme output in response to vagal stimulation with 2-deoxy-D-glucose was reduced by 75% in those dogs whose vagal-gastrin mechanism was eliminated but was only slightly diminished in canines with an intact vagal-gastrin mechanism. These studies suggested that a major part of the pancreatic response to sham-feeding was mediated by the vagal release of gastrin. It does not follow that gastrin is a major mediator of the sham-feeding response, inasmuch as 2D-G is not equivalent to sham-feeding. Other experiments, however, have demonstrated cephalic control of gastrin release as measured by radioimmunoassay. It has been reported that electrical stimulation of the vagi in the dog[35, 36] and the cat,[37] insulin-induced hypoglycemia in the dog[38] and sham-feeding in the dog[39, 40] increased serum gastrin levels. Gastrin pentapeptide stimulates the pancreas as the pentapeptide dosage necessary to elicit a maximal acid response from the stomach is approached.[44] In dogs with chronic fistulas Gastrin I,[42] porcine gastrin[44, 45] and pentagastrin[43, 45-47] markedly increase the pancreatic protein output.[42-47] On the basis of dosage, both pentagastrin and gastrin equally augment pancreatic protein output but pentagastrin causes a greater pancreatic bicarbonate response.[43] Indeed, the exocrine response of the pancreas to a meat meal, as measured by the protein and bicarbonate outputs, could be reproduced by pentagastrin infusion.[47] On the other hand, injections of gastrin did not augment the secretin effect on the pancreas and potentiation between gastrin and secretin could not be demonstrated.[44] When dogs with chronic pancreatic fistulas were subjected to bilateral vagotomy, they demonstrated an increased sensitivity of the pancreas to pentagastrin stimulation as measured by protein and bicarbonate outputs.[46] In addition, chemical stimulation of the isolated innervated canine antral pouch with 10% alcohol increased the pancreatic amylase output and volume after a 10-30-minute latent period.[48] Finally, a direct effect of gastrin on the pancreas was demonstrated in the perfused isolated canine pancreas. Pure Gastrin II and gastric antral extracts increased the pancreatic flow, trypsin, chymotrypsin and amylase outputs.[49] These experimental data leave little doubt that gastrin stimulates pancreatic exocrine secretion in most animal species. Is this action pharmacologic or physiologic? How significant is this action in terms of the integrated meal response?

## HUMAN PANCREATIC EXOCRINE FLOW

Examination of the literature reveals that the responses of the exocrine pancreas in man to gastrin are more variable because of the greater difficulty in collecting pancreatic juice. With one exception, all studies of pancreatic secretion have collected juice by suction from the duodenum. Graded doses of pentagastrin alone usually had no effect on pancreatic bicarbonate[50-53] nor on proteolytic enzymes.[50-53] In one study,[54] however, pentagastrin maintained the pancreatic flow and increased the total enzyme output by a slight rise in enzyme concentration. This response differs from canine sham-feeding[33] in which the enzyme concentration is maximally effected and suggests a mechanism other than direct gastrin stimulation. In studies in which constant flow is maintained by secretin infusion, pentagastrin administration in man augmented the pancreatic volume,[55, 56] the trypsin output[55, 56] and the bicarbonate.[55] In other studies with similar protocol, however, no effects on the pancreatic volume,[57] the bicarbonate[51, 56, 57] or the proteolytic enzymes[51] were reported. In those investigations in which cholecystokinin was constantly infused in man, pentagastrin did not modify the bicarbonate[50, 52] nor the proteolytic enzymes[50, 52] output. Under similar conditions, however, a synthetic gastrin tetrapeptide was noted to increase the amylase and trypsin outputs.[58] When both secretin and cholecystokinin were infused, pentagastrin had no effect on the bicarbonate output[59] and inhibited the proteolytic enzymes[59] response. Endogenous release of gastrin by balloon distention of the stomach in control subjects and in patients with chronic pancreatitis, elicited no change in pancreatic flow or bicarbonate but did produce a delayed increase in lipase and trypsin output.[60] Finally, in the one study[61] in which the exocrine secretion was collected from an external pancreatic fistula, pentagastrin consistently increased pancreatic flow.

There are a number of ways these disparate human data can be explained. First, pancreatic juice collection by small bowel suction is not very accurate so that a collection error may account for the variable results. Yet when the bicarbonate responses to synthetic little gastrin was studied using a marker for collection corrections,[62] gastrin augmented the human pancreatic exocrine secretion. The discordant data might also result from the possibility that the reported responses of the exocrine pancreas were not caused by gastrin *per se* but by other factors so that gastrin might have little or no effect on the human exocrine pancreas. The evidence for such an hypothesis is not good.

Until recently, little attention had been paid to the exocrine pancreatic function in the Zollinger-Ellison syndrome. Some of the earlier duodenal drainage studies on these patients reported a reduced basal enzyme activity,[63, 64] no duodenal trypsin activity after injections of cholecystokinin[65] or after a meal,[66] or slight transient increases in duodenal bicarbonate after injections of secretin.[65] Other duodenal drainage reports indicated normal basal amylase activity,[67] trypsin activity[67] and bicarbonate concentrations,[68] normal bicarbonate responses to a meal[66] and to secretin injections,[69] normal amylase activity to secretin-cholecystokinin injections[69] and normal trypsin activity to a meal.[66] More recent studies have shown that when patients with the Zollinger-Ellison syndrome were compared to control subjects they had elevated basal flow and bicarbonate levels[70, 71] and that secretin injections markedly augmented the pancreatic fluid and bicarbonate levels.[68, 70, 71] It was, therefore, postulated[70] that the hypergastrinemia of the Zollinger-Ellison patient resulted in a very marked elevation in gastric acid secretion with a lowering of pH levels in the upper small bowel and a continuous release of endogenous secretin and cholecystokinin. These data, however, do exclude a direct ecbolic effect of elevated serum gastrin levels on pancreatic acinar tissue. The pathophysiology would be greatly clarified by pancreatic secretion studies in Zollinger-Ellison patients whose pancreatic tumor(s) had been left intact but who had been subjected to total gastrectomy with a gastroduodenostomy.

## TROPHIC INFLUENCE ON THE PANCREAS

This chronic administration of pentagastrin to rats causes hypertrophy of the pancreatic acinar cells with no increase in the acinar cell nuclear count, an increase in the RNA:DNA ratio and a decrease in the specific activities of pancreatic enzymes.[72] The chronic administration of pentagastrin to hypophysectomized rats prevents decrease in pancreatic weight and decrease in the RNA:DNA ratio.[73, 74] It is postulated, therefore, that pentagastrin increases the cytoplasmic content of the acinar cells, e.g. produces hypertrophy. Further studies are needed to elucidate the importance of pancreatotrophic development and activity of gastrin, i.e. in the development, the maintenance of pancreatic size and the composition of pancreatic juice.

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# Transverse Taeniamyotomy in Localized Acute Diverticulitis

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Transverse taeniamyotomy has been in use for over four years in the surgical correction of the muscle abnormality of diverticular disease. Essentially, the technic is to carefully transversely incise the two antimesenteric taeniae coli at 2 cm. intervals, in a stepwise manner, from the rectosigmoid junction proximally up to normal colon. This causes the cut ends of the taeniae coli to pull apart into separate 2 cm. blocks of longitudinal muscle. Thus elongation and widening of the colon occurs, resulting in dilatation of the necks and free drainage of the diverticula obstructed by inflammation. Four patients are presented with localized diverticulitis who had simple transverse taeniamyotomy from which they quickly recovered. This operation justifies continuing study as it may increase the surgeon's range of response over one end of the spectrum of acute diverticulitis.

## INTRODUCTION

There is a continuing controversy over the surgical management of acute diverticulitis. For many years the only surgical treatment was colostomy and drainage until Smithwick[1] pointed out in 1942 that diverticulitis recurred if the affected segment was not subsequently removed. Therefore, staged procedures have been carried out. The first was transverse colostomy and drainage of the sigmoid; the second, after about six weeks, sigmoid resection and anastomosis; the third, after a further six weeks or so, closure of the colostomy. It is clear that a considerable time in hospital is required to undergo these three procedures and this unsatisfactory situation is worsened by the considerable morbidity and mortality which also occur.[2, 3]

In a leading article in the British Medical Journal[4] it was recently pointed out that transverse colostomy and drainage has often proved ineffective in treating a free perforation and is inappropriate in localized acute diverticulitis which often responds to initial treatment with antibiotics and intravenous fluids. Such patients may then be assessed at leisure and a decision made on whether elective surgery is needed. Immediate resection by a skilled surgeon was recommended in diverticulitis with free perforation and resection and primary anastomosis was recommended for localized disease. There may be a place, however, for the use of transverse taeniamyotomy in localized acute diverticulitis

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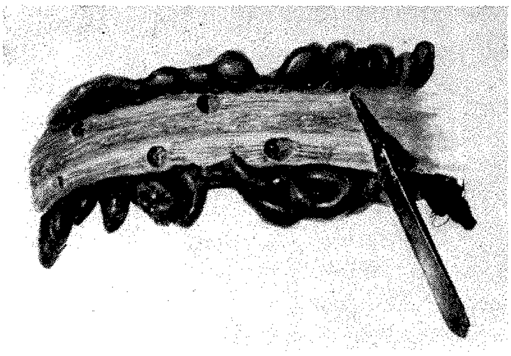

Fig. 1—Transverse taeniamyotomy.

as it is a simple and benign operation and this paper presents a pilot study carried out in four carefully selected cases.

## METHOD

Transverse taeniamyotomy (Fig. 1) is most easily performed on the sigmoid colon through a left lower paramedian incision but can be done through any incision which gives adequate exposure. First, the sigmoid colon must be mobilized and this was done by incising along the bloodless lateral peritoneal fold of Toldt from the descending colon to the rectosigmoid junction.

Cephalad traction was then applied to the sigmoid colon and after identification of the two thickened antimesenteric taeniae coli, a No. 15 blade was used to make multiple transverse incisions through them. These incisions were commenced just below the rectosigmoid junction and then further incisions were made proximally at 2 cm. intervals, in a stepwise manner, through the thickened antimesenteric *taeniae coli* only, until normal *taeniae* were encountered in the descending colon. Each incision was done with extreme care and sometimes a peanut was necessary to ensure all longitudinal fibers were divided. There was little bleeding for the integrity of the submucosa was not compromised and there was no danger of perforation.

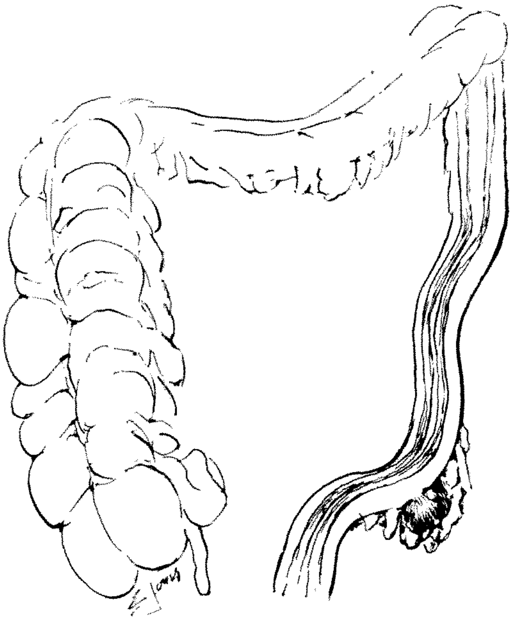

Fig. 2—Drawing of localized diverticulitis in Case 1.

Under no circumstances should a cautery be used on the colon; hemostasis was normally achieved by a little applied pressure and an occasional vessel needed a catgut tie. Finally the sigmoid colon was replaced on the lateral abdominal wall and the abdomen was closed without drainage.

## CASE REPORTS

*Case 1:*—This 68-year old white male was admitted with a three-day history of constipation and increasing crampy abdominal pain. He had had milder episodes of pain and constipation on and off for the previous six years.

On examination he was considerably overweight; his pulse rate was 112 and his temperature was 38° C. He was tender in both lower quadrants but more on the left side than on the right. His WBC was 11,800 and fell to 7,300 after two days on Ampicillin. His abdominal x-rays showed an ileus. He responded to treatment and a barium enema was done which showed diverticular disease with spasm in the recto-sigmoid area. A diagnosis of long-standing diverticular disease was made on which an attack of diverticulitis was superimposed.

Ten days after admission, as he was still tender and had a palpable mass in the left lower quadrant, operation was performed. He was found to have considerable thickening of the muscle of the sigmoid colon and in the lateral wall of the sigmoid was an inflammatory mass about 5 cm. in diameter (Fig. 2). Because this area of diverticulitis was so circumscribed it was decided to perform transverse taeniamyotomy alone and this was done. The postoperative course was benign and a repeat barium enema showed much improvement. He was discharged on a high fiber diet but has not kept to it. He appeared well 16 months later.

*Case 2:*—This 87-year old white male was admitted with a history of passing three bloody stools in the previous 24 hours. He also had right and left lower quadrant pain for three days and had been known to have diverticular disease for one year. Four years before he had had a cholecystectomy and 16 years before admission he had a prostatectomy.

On examination he was pale, with some lung congestion. He had a 3 × 5 cm. sausage-like mass in the left lower quadrant which was tender. A presumptive diagnosis of diverticulitis was made. He continued to have rectal bleeding and developed a questionable infiltrate in the right lower lobe of his lung.

A barium enema showed severe diverticular disease but the preparation was less than ideal. Several unsuccessful attempts were made at colonoscopy.

He developed a urinary tract infection, his bleeding continued and he developed a right lower lobe infiltrate. He had now been in the hospital for one month and his situation had become critical on his medical treatment. It was decided that surgery was indicated before he deteriorated further.

At operation the source of his bleeding was found to be a large ulcerated follicular lymphosarcoma 10 × 8 × 6 cm. in the ascending colon and there was extensive lymph node involvement. A right hemicolectomy was performed. He also had sigmoid diverticular disease and on the medial aspect there was an inflamed area of diverticulitis measuring 4 × 3 cm. A transverse taeniamyotomy was performed for the sigmoid pathology.

Postoperatively the patient was extubated on the eight day and was put on full fluids. A week later he developed a further attack of right lower lobe pneumonia and was re-intubated. He began to improve but had an anterior wall myocardial infarction.

He continued to require respiratory support for a further two months but there had been no surgical problems for some time as his gastrointestinal tract was clinically normal and there was no evidence of recurrent diverticulitis. During this time he was fed on Isocal through a nasogastric tube. Accordingly he was transferred to the Medical Service. Two weeks later he died of respiratory failure due to a total right lung pneumonia. Permission for autopsy was not granted.

*Case 3:*—This 82-year old white male was admitted with approximately a two-day history of abdominal pain and distention.

On examination the patient was pale with a markedly distended abdomen in part due to ascites but it was tympanitic and no masses were palpable. There was

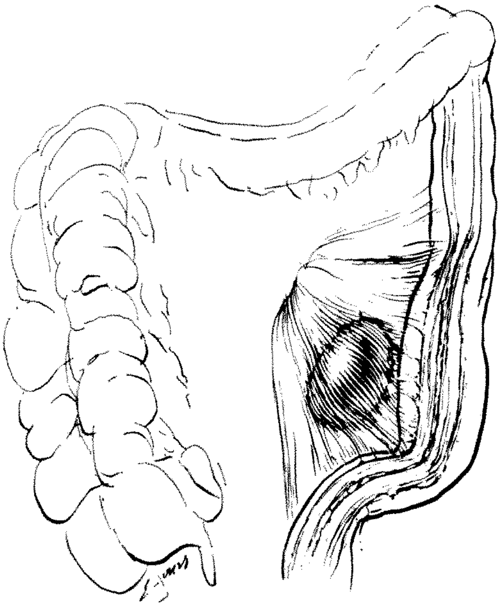

Fig. 3—Drawing of localized diverticulitis in Case 3 showing perisigmoiditis and intramesenteric abscess.

diffuse tenderness. Bowel sounds were high pitched. Rectal examination was negative. X-rays showed only dilated small-bowel loops and his WBC was 6,300. Hgb. was 8.2 gm.% and his hematocrit was 23. Electrolytes were normal.

The patient received supportive treatment including I.V. fluids and nasogastric suction but the pulse continued to rise and there was no abatement of his abdominal pain and distention. Therefore, after 24 hours, laparotomy was performed which revealed a grossly cirrhotic liver, ascites and a mass in the mesentery of the sigmoid colon which had multiple diverticula. The mass was hard, nonfluctuant and the mesentery around it was thickened (Fig. 3). It was thought that the mass was an abscess in association with the grossly inflamed sigmoid which was plastered to the side wall of the abdominal and pelvic cavities.

Because of the possibility of ascitic leakage from alongside a colostomy, the decision was made to mobilize the sigmoid colon and simply perform a transverse taeniamyotomy over the entire sigmoid including the inflamed area. This was done carefully and uneventfully.

Postoperatively the patient had settled within 48 hours. After one month, the patient was discharged from the hospital, stable with an abdomen distended by ascites but nontender, and with a normal bowel action. He was well one year later.

*Case 4:*—This 60-year old man had diverticulitis for many years for which he had had a right transverse colostomy performed. One year later he developed a bladder calculus which was removed. Six months later his colostomy was becoming a nuisance and he wanted it closed. Hemoglobin, white count and blood chemistry were normal but he did have bilateral renal calcification. A barium enema showed a normal ascending and transverse colon but scattered diverticula were present in the left colon. Also there were two sinus tracts about 1 and 1.5 cm. long in the rectosigmoid area which suggested signs of continuing diverticulitis. Severe plication was also present with narrowing. There was no mechanical obstruction.

At operation there was some chronic inflammation of the rectosigmoid mesentery. It was decided to perform a transverse taeniamyotomy and this was done from the rectosigmoid junction up to the descending colon. It was noted that the *taeniae coli* were thickened, especially at the rectosigmoid area where they were 0.5 cm. in size. Finally the transverse colostomy was closed to conclude the operation.

The postoperative course was so uneventful with the patient quickly recovering that it was possible to discharge him after seven days. He remained well six months later.

## COMMENT

It is suggested that a dynamic approach is adopted in the treatment of acute diverticulitis which depends on the severity of the inflammation. Thus localized diverticulitis may be adequately treated with antibiotics and intravenous fluids. When this approach is inadequate, surgery is required. The dynamic approach might call for transverse taeniamyotomy as the procedure of choice in localized acute diverticulitis, resection with anastomosis when extensive peridiverticulitis is present and staged resection with later anastomosis when there is abscess formation or free perforation.

Transverse taeniamyotomy was introduced in 1973 as a rational simple surgical procedure[5] to reverse the colonic shortening with plication and narrowing which occurs as a consequence of the muscular abnormality of diverticular disease.[6] From animal work[7] it was suggested that the procedure would release this fixed plication with increase in colonic diameter and reduction of diverticula. This effect did occur in patients after transverse division of the *taeniae coli,* and as the cut ends pulled apart, the colon lengthened, its diameter increased, most diverticula disappeared and those remaining had their necks opened widely.[8] In acute diverticulitis, studies of pathological specimens have revealed perforation of diverticula which may be free or microscopic.[9] Possibly this followed inflammatory obstruction of the neck of the diverticulum. Perhaps because transverse taeniamyotomy elongated and widened the colon in localized acute diverticulitis, the diverticular necks were opened sufficiently to allow free drainage of the diverticulum and its associated abscess into the colonic lumen before perforation, thus reducing the chance of fistula formation. Furthermore, as the *taeniae coli* only were divided and diverticula are situated laterally in the colon, the risk of entering an inflamed diverticulum was minimal.

Transverse taeniamyotomy is much simpler to perform than the longitudinal myotomy which was introduced in 1964 by Reilly[10] when he intuitively proposed that symptoms and complications of diverticular disease could be abolished without resection of the thickened bowel using a technic similar to Heller's cardiomyotomy or Ramstedt's pyloromyotomy. Arfwidsson[11] was immediately critical of this innovation, pointing out that theoretically the *taeniae coli* must be cut transversely if lengthening of the colon is to occur. In practice, the longitudinal myotomy has proved to be a very difficult operation to perform because the knife cuts at right angles to the plications of the colon, and across the submucosal plexus so that hemostasis may sometimes only be obtained at the expense of mucosal perforation. Omental patches[12] and routine cecostomies[13] have been used as complimentary procedures but still the morbidity[13] and mortality[14] was unacceptable for a purely elective procedure used, as Reilly indicated after five years' experience,[15] in chronic diverticulitis or diverticular disease. In consequence, the longitudinal myotomy has fallen out of favor.

The transverse taeniamyotomy, on the other hand, has not had such problems. Following its first introduction as a more rational surgical approach for diverticular disease,[5] it was also employed by Hodgson[8] in the presence of severe inflammation. In that instance a 46-year old white male presented with a 48-hour history of peritonitis from his perforated diverticulitis. As the patient refused a colostomy, a sigmoid resection with primary anastomosis was performed, associated with proximal and distal transverse taeniamyotomies. Although colostomy was done after 48 hours to deflate the colon dilated secondary to the peritonitis, his anastomosis and taeniamyotomies were intact and he subsequently did well. Therefore, in Case 1, since the area of diverticulitis was a locally circumscribed mass in a pericolic situation and the patient had not responded to the standard nonsurgical routine, it was felt that adequate surgical treatment could be obtained by transverse taeniamyotomies which would be close to but not through, the inflamed area.

Because of the successful response to transverse taeniamyotomy in Case 1, the dilemma in Case 2, that is a right-sided cancer and a left-side diverticulitis, was easy to solve. Despite strenuous efforts to detect the exact source of bleeding the only definite preoperative finding was that of diverticular disease. At operation a right hemicolectomy was performed for his follicular lymphosarcoma and an area of diverticulitis was seen. As hemorrhage occurs to some degree in approximately 30% of patients with diverticulitis,[16] a further procedure was required. Hodgson[8] has already demonstrated that the transverse taeniamyotomy can safely be done in association with right hemicolectomy for cancer, and this double procedure was therefore carried out satisfactorily in this patient.

In Case 3, the patient was a sick man and required urgent surgical intervention. His ascites made colostomy formation a hazardous procedure and the intramesenteric abscess increased chances of leakage from primary resection with anastomosis. On the other hand, the basic pathology in this case was an intramesenteric and not a free perforation of a diverticulum so transverse taeniamyotomy, by allowing intracolonic drainage of the abscess, became the operation of choice.

Case 4 followed naturally. It was necessary to close the colostomy because it was troubling the patient and roentgenological evidence showing diverticular disease with continuing diverticulitis demanded definitive treatment. His lack of systemic or local signs convinced us that he would be adequately and simply treated with transverse taeniamyotomy and colostomy closure. His benign postoperative course confirmed our reasoning.

Our view coincides with a recent editorial[4] that the dynamic approach and the management of diverticulitis allows the simplest successful treatment to be used whenever possible and is preferable to the dogmatic approach that a three-stage procedure is always used. It should be borne in mind that each step of a staged procedure carries its own mortality and the cumulative mortality in the last decade has varied from 11-26%.[17, 18] The time in hospital for all three stages averages about three months[18] although the third stage has often been postponed indefinitely due to the poor health of the patient.[17-19] It is not always easy, in retrospective studies, to be sure of the exact pathology in each case but in one study[19] cases with abscess formation were separated. Here, a mortality of 39% occurred.

The poor over all results in the surgery of diverticulitis must be improved. This pilot work indicates that a simple procedure, the transverse taeniamyotomy, is available for study in diverticulitis, either as a primary procedure in localized disease or to telescope the second and third stages of conventional surgery which may then be compared in a trial to the standard three-stage procedure.

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# Be Aware of Gardner's Syndrome

## A REVIEW OF THE LITERATURE

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## INTRODUCTION

A classical case of Gardner's syndrome is presented. An extensive review of the literature with the multiple varieties, presentations and hereditary factors of this familial disease are discussed.

The importance of early diagnosis with careful scrutiny of the past and present family, searching for cutaneous and osseous manifestations that accompany, on many occasions, silent polyposis of the colon plus adequate radical therapy are stressed.

## CASE REPORT

Recently, a patient, 52 years old, came to the gastroenterology clinic of our hospital with a complaint that sometimes is taken lightly: "my two brothers died of cancer of the bowel recently . . . I would like to be checked". The patient was completely asymptomatic. Physical examination revealed multiple but discrete soft tissue abnormalities (Figs. 1 and 2) and a hard, also discrete lesion in a long bone of the lower extremity. He had a history of having a large soft tissue mass removed from his forehead in 1950. Proctosigmoidoscopy revealed multiple (1-2 mm.) polyp lesions covering the rectum and colonoscopy showed total involvement of the colon (Fig. 3). Biopsies of the polyps were reported as adenomatous polyps with no evidence of malignant transformation. Biopsies of the skin lesion showed fibroepithelial polyps, squamous papilloma and epidermal cysts. Upper gastrointestinal series and endoscopy, small bowel series and barium enema examination were all normal. Roentgenogram of the right lower extremity revealed osteoma in the distal fibula (Fig. 4). The patient's family was contacted and examination of the siblings revealed the family tree print shown in Figure 5.

Within one month two brothers of our patient had died of carcinoma of the colon with metastatic disease. None of them had osseous nor skin abnormalities. One of the two had a previous surgery for polyposis with ileoproctostomy, and developed carcinoma in the anastomotic area several years later. The father of our patient died at age 83 of "old age" and the mother died at age 58, apparently due to a liver ailment. That brings out the possibility of this being a metastatic disease to this organ. Out of nine children in this generation, one died in an accident at age 6. Of the remaining eight, five of them have proven polyposis

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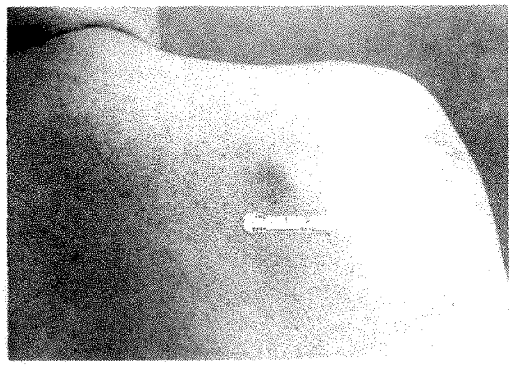

Fig. 1—Epidermal inclusion cyst of the right scapular area.

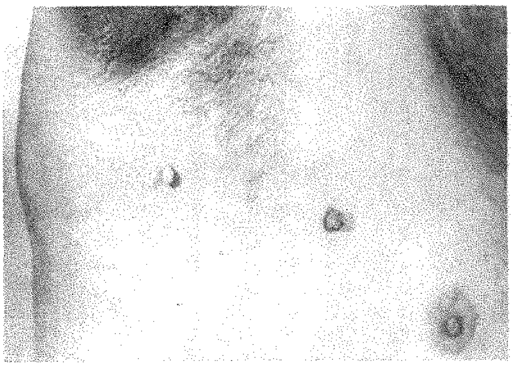

Fig. 2—Fibroepithelial polyp and squamous papilloma of the right axilla.

but only our patient has osseous or cutaneous tumors in this generation.The youngest generation is presently being scrutinized.

Our patient has been offered the alternative of total colectomy with ileostomy or with ileoproctostomy and considering all the possible consequences, he elected, to our satisfaction, to undergo total colectomy with ileostomy.

## Review of the Literature

Multiple polyposis of the colon was reported first by Menzel in 1721 quoted by Bochetto, et al; described for the first time by Virchow in 1863 and not until 1882 was its familial occurrence pointed out by Cripps, quoted by Bochetto, et al and Simpson, et al.[2] A series by Smith[3] in 1958 accounts for 8.5% of patients with familial polyposis who have external manifestations of Gardner's syndrome and in 1964, a series by Simpson, et al[2] accounts for as many as 60% of them. If this information is correct, from 1863 to 1950, when Gardner described the constellation of findings that concur in his patients, there had been thousands of patients with this disease that went unrecognized until it was too late. From a clinical standpoint, the association of subcutaneous tumors and osteoma should lead to a strong suspicion of polyposis of the large bowel.[4-7]

It is now known that the external manifestations in these patients occurred long before the gastrointestinal disease was discovered.[8, 9] It could have been life-saving for many of these patients had regular screening with endoscopic examinations[10] and careful familial history been obtained on the basis of suspicion when the clinician was faced with the skin and bone manifestations of this disease.

Gardner[11, 12] described in 1950 a group of patients that belonged to the same family, in whom a series of soft and hard tumors occurred concomitantly with multiple polyposis of the colon. Invariably these polyps advanced to malignancy.

Since then many different types of tumors, benign and malignant, have been described in association with polyposis of the colon and looking back in the literature, there were several other isolated reports before Gardner's description. In 1937, Miller and Sweet reported a case of fibrosarcoma, leiomyoma, desmoid, epidermal cyst, and bony exostosis associated with multiple polyposis of the colon as quoted by Gorlin and Chaudhry.[13] Pugh in 1945 described a case of mesenteric fibrous tissue and multiple polyposis of the colon. Clark

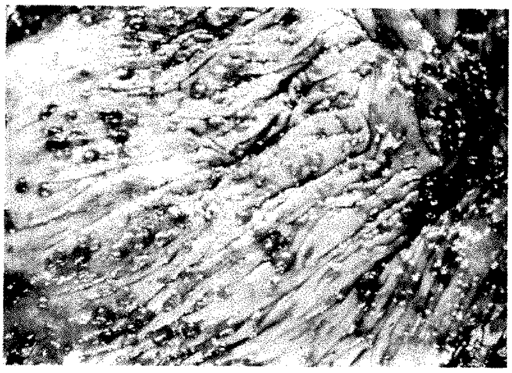

Fig. 3—Multiple 1-2 mm. polyps covering the rectum and entire colon.

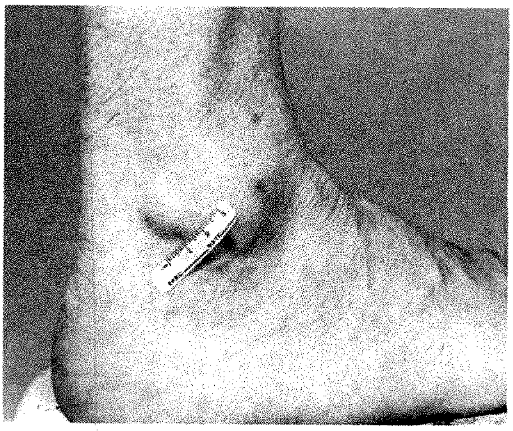

Fig. 4—Osteoma, right distal fibula.

and Parker, quoted by Laberge, et al,[14] found a case with three retroperitoneal leiomyomas and multiple polyposis in 1950.

Since Gardner described the syndrome that now bears his name, many other lesions have been described in association with multiple polyposis of the colon. Among these are: multiple supernumeraries and impacted teeth; polyposis of the small intestine and stomach, fibromas, desmoids and poorly differentiated connective tissue tumors;[1, 6] tumors in the mesenteric and retroperitoneal areas[15] and Simpson, et al, reported two cases of breast fibromatosis associated with intestinal polyposis.[2] Another curiosity, found in people with this disease, is an abnormal proliferation of connective tissue, that is more evident at the level of the scars, sometimes to the point of causing intestinal obstruction due to adhesions. Simpson, et al reported a case of a 3,815 gm., 30 × 30 × 13 cm. fibrous, compact, benign mass in a patient who had previous surgery for multiple polyposis of the colon.[2]

Schiffman, et al, reviewed 90 cases of familial polyposis with hard and soft tissue tumors and found that 43% had osteomas, 37% sebaceous cysts, 17% desmoid tumors, 12% fibromas and 11% fibrous tissue masses and lipomas.[16]

A very unusual presentation was described by Lynch, in which an overlapping of nevoid basal cell carcinoma syndrome (NBCC) and Gardner's syndrome was present. This was a 40-year old patient with multiple basal cell carcinoma, mandibular cyst, calcification of the *falx cerebri,* palmar pits, bridging of the *sella turcia,* keratinous cysts of the skin, cryptorchidism and chalazium, all belonging to the NBCC syndrome but also presenting with Grave's disease and multiple polyposis of the colon.[17]

Other unusual forms of presentation include several cases of polyposis of the duodenum with carcinoma and associated with skin tumors; five cases of periampullary carcinoma, reported by Coli, et al, with absence of polyps but presence of skin manifestations of Gardner's syndrome[6] and a case of two sisters, reported by Camiel, et al, that presented with full blown Gardner's syndrome and thyroid carcinoma.[18]

Bone tumors in Gardner's syndrome are mostly osteomatosis and exostosis,[19] that occur mostly in the skull and facial bones, having preference primarily for the maxilla and mandible, followed by ethmoid, sphenoid and frontal sinuses and in some cases even producing nasal obstruc-

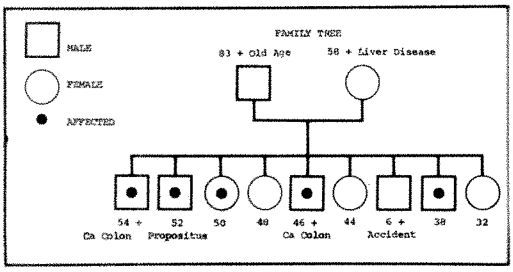

Fig. 5—Family tree of patient reported.

tion. This does not mean that they occur exclusively in this area but they can be present in long bones as well. The radiographic findings are varied. They present thickened and undulating cortices, dense lobated projections that may be pedunculated or sessile, impacted permanent and supernumerary teeth and multiple small rounded areas of increased density of uncertain significance, that most likely represent small foci of hyperplastic bones. Also, the long bones may be slightly shortened and bowed and have been described most commonly in radius, ulna, femur, tibia and fibula but they may also occur in other bones.[20, 21]

At first, the polyposis is usually asymptomatic and remains so for many years, until diarrhea, abdominal pain, tenesmus, blood and mucus in stools appear. The polyps are usually present in all the colonic mucosa and can also occur in patchy areas. McKusick has said that polyps in Gardner's syndrome are multiple but scattered and that they do not blanket the colon completely, as they do in familial multiple polyposis.[22] After reviewing many of the cases published and our own, this does not appear to be the case. McKusick also notes that the polyps may occur in any place in the gastrointestinal tract and not so in familial polyposis. The polyps may affect the small intestine and the stomach.[1, 23] They are usually small in size (1-2 mm.), adenomatous in type and may be pedunculated or sessile. Multifocal malignant transformations occur in 100% of them.

The incidence of Gardner's syndrome is 1/8,300-1/16,000 births. It can occur at any age, and has been reported as early as two years of age and as late as 70 years old.[1] Generally the external, dermatologic and osseous manifestations appear very early in life, with the polyposis appearing between ages 25-35 and its malignant transformation, approximately 15-20 years later. Sometimes the patient is totally asymptomatic until it is too late.

There seems to be total agreement that the polyposis is transmitted as a dominant gene affecting both sexus equally and that half of the children of an affected parent have the disease and all the children of those parents not affected are normal.[11, 24] Dawborn, et al[5] and Stanley[25] suggest that the disease is transmitted by a single autosomal gene capable of expressing itself as the clinical trait in the heterozygous state in a large percentage of cases. The abnormal gene may develop as a genetic mutation in the mother. It is definitely not sex linked. Smith, et al explain the pattern of inheritance of all elements by a single dominant pleotrophic gene. The homozygous behavior of the disease is not known, since no two affected persons have married. The inheritance of the subcutaneous lesions appears complicated by the different kinds and apparently unrelated abnormal surface growths in the members of a given family.[26] One hypothesis is that closely linked second and third genes, with poor penetrance, may account for the osteomas and subcutaneous lesions in some and the absence of these in other members of a same family.[9, 13, 27]

Early diagnosis and prophylaxis appears to be of utmost importance in the treatment of this syndrome in order to avoid the malignant transformation of the polyps. Recent work, by Pfeffer, et al, on skin fibroblast growth, appears to show a characteristic type in patients with adenomatosis of the colon and rectum.[28] In the future, this could be used as a screening test to determine the progeny of an affected parent and depending upon the result, adequately counsel the follow-up and genetical implications.

In all the bibliography reviewed, the only procedure that seems to be life-saving, if used early enough, is total colectomy with ileostomy. In practically all cases in which proctostomy was performed, tumors appeared later in the area of anastomosis. All cases not resected underwent malignant transformation.

Gardner's syndrome is only one of the many diseases that present a combination of soft tissue abnormalities and bowel disease. Why an ectodermic and an endodermic structure associate so frequently, has puzzled many authors. Owens[29] in 1969 published 35 different diseases that involved the skin and the bowel. Reed, et al,[30] published an article discussing 46 diseases of the skin that are associated with nonmalignant and malignant tumors of the bowel.

The skin-gut association becomes a very important fact to be taken into consideration at the time of physical examination. The tumors of the skin and osseous lesions occur so early in Gardner's syndrome, in relation to the polyposis, that they could be a guiding light to the examining physician. Following this guide, a careful family history, and regular endoscopic examinations of patients approaching the "dangerous age" for appearance of the polyps, could be of extreme value. Once the polyps are found, aggressive radical therapy and examination of the patient's relatives, could represent saving the lives of many individuals.

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***Clinical Vignette***

# Pancreatic Carcinoma Difficult to Differentiate from Duodenal Carcinoma

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A case of carcinoma of the uncinate process of the pancreas that was clinically misdiagnosed as primary carcinoma of the duodenum is reported. This is a rare case because the cancer infiltrated the duodenum producing a large tumor with central ulceration, well-defined rolled-up margins giving the appearance of a typical gut adenocarcinoma. Although the carcinoma of the pancreas is more common than the duodenal carcinoma, we wish to describe why the misdiagnosis has been made.

## Case Report

A 61-year old male was transferred from another hospital and was admitted for further diagnostic study. Prior to admission he had had an upper gastrointestinal series which disclosed an apple core-like filling defect at the second portion of the duodenum without widening of the duodenal loop (Fig. 1).

On admission he was not jaundiced. An immobile egg-sized, firm, tender tumor was palpable in the right upper quadrant of the abdomen. Routine laboratory examination disclosed the stool was strongly positive for occult blood; urinalysis was normal; complete blood count showed slight normochromic anemia; blood chemistry showed slight increase of total bilirubin (1.5 mg./100 ml.); slight elevation of transaminase (SGOT, 90U.; SGPT, 66U.), increased of alkaline phosphatase (81.5 K-A units) and high blood amylase (435 Blue-

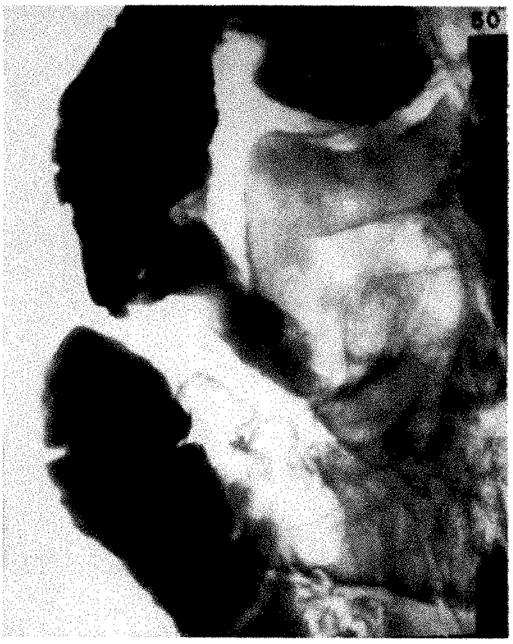

Fig. 1—Upper gastrointestinal series, showing napkin-ring like filling defect at the second portion of the duodenum without widening of duodenal loop (spot film).

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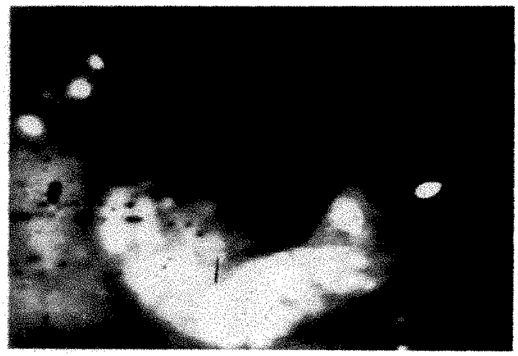

Fig. 2—Duodenoscopy, showing a large tumor with central ulceration.

Strach units). Alphafetoprotein, HB-Ag and TPHA were all negative.

The pancreas scintigram showed clearly and well visualized pancreas. The $I^{131}$-BSP scintigram showed no biliary obstructive pattern. A duodenoscopic examination disclosed a large tumor with central ulceration in the second portion of the duodenum. This tumor seemed almost annular so that further instrumentation was possible. The papilla of Vater could not be found (Fig. 2).

A biopsy specimen, obtained from the tumor, showed moderately differentiated adenocarcinoma. The celiac and superior mesenteric angiogram failed to reveal any abnormality in the pancreas. From these findings a diagnosis of primary duodenal carcinoma was made.

A month later, laparotomy was performed but the patient developed shock during the general anesthesia. Only cholecystectomy and choledochoduodenostomy could be done. Ten days after operation, he was placed on chemotherapy and was discharged. He was then followed as an outpatient. Three months later, the patient developed severe anorexia and was readmitted. After a month of hospitalization, he developed fever and jaundice. The downhill course was rapid. He expired eight months after his first visit to our institute.

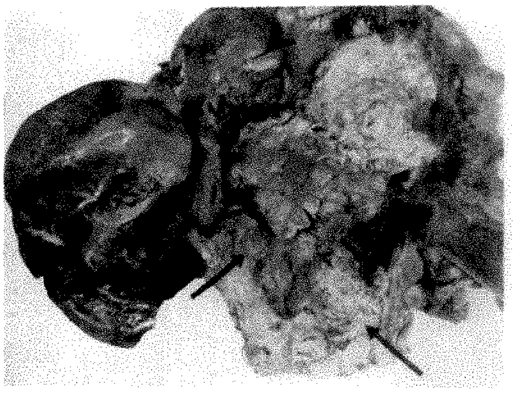

Fig. 3—Cut surface of the tumor in the uncus and head of the pancreas and duodenum. Note complete destruction (arrows) of the third and second portions of the duodenum.

At autopsy, a fist-sized tumor was found (Fig. 3) at the uncinate process and head of the pancreas, invading the descending and horizontal part of the duodenum. Microscopically, many different patterns of adenocarcinoma, such as medullary, cribiform and mucinous, were seen, although the medullary pattern predominated (Fig. 4).

## COMMENT

The main tumor was located in the uncinate process of the pancreas. It seemed proper, therefore, to conclude that this was a case of carcinoma of the pancreas massively infiltrating the duodenum and producing a large intraluminal tumor with central ulceration.

In necropsy studies the incidence of carcinoma of the duodenum is 0.01-0.04%.[1] It comprises 0.3% of all gastrointestinal carcinomas[2] and 45% of those of the small intestine.[3] On the other hand, in most autopsy series carcinoma of the duodenum accounts for about 2% of all cancers,[4] whereas pancreatic carcinoma ranks fourth in men and sixth in women among the causes of death from cancer in the United States.[5] Moreover, the mortality rate from

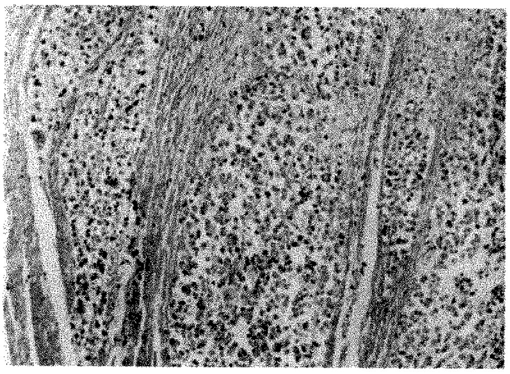

Fig. 4—Infiltration of cancer cells into the muscle layers of the duodenum, showing medullary pattern (Hematoxylin and eosin, original magnification x160).

pancreatic cancer is increasing in the industrial countries including Japan.[6-9] In most series, there are no statements as to whether the carcinoma arises from the head or from the uncinate process of the pancreas. Occurrence in the uncinate process is rare, however; only three of 45 cases selected by us at random, died from pancreatic cancer; in an autopsy series the incidence was less than 0.07%.[10] Carcinoma of the pancreas is clinically classified into two types, i.e. arising from the head or from the body and tail. It is generally accepted that about two-thirds of the carcinomas originate in the former and one-third in the latter.[11, 12]

In nine years from 1966-1974 at our institute, autopsies of 40 cases of pancreatic carcinoma were performed. Although 20 of these showed infiltration of carcinoma to the duodenum, 17 (95%) originated from the head and infiltrated to the second portion and only three originated from the body or tail and infiltrated the third portion. Cancer infiltration of the duodenum by the pancreatic carcinoma was generally not massive or extensive. Since in these 20 cases, the endoscopic appearance was that of simple erosion, these cases were correctly diagnosed before autopsy. Only four cases of carcinoma of the pancreatic head disclosed no cases of duodenal infiltration. During the same period, no primary duodenal carcinoma, excluding carcinoma of the papilla of Vater, was noted at autopsy in our institute. Thus, this was an unusual case misdiagnosed despite the extensive preoperative investigation. The infiltration of the duoendum by pancreatic carcinoma produced a large tumor with deep central ulceration. This finding and the lack of clinical symptoms made diagnosis difficult. Yet it must be stressed that neoplasms of the second part of the duodenum may have the same clinical symptoms as tumors of the ampulla of Vater, the head of the pancreas and the biliary tract,[13, 14] so that accurate diagnosis of these tumors can often only be made at the autopsy table.

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***Clinical Vignette***

# Mediastinal Pancreatic Pseudocyst

## AN ULTRASONIC DIAGNOSIS

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Mediastinal extension of pancreatic pseudocysts is uncommon. Frequent presenting complaints include chest pain and shortness of breath. Dysphagia is rare. A patient with mediastinal pseudocyst causing dysphagia is presented. The role of gray-scale ultrasound as a reliable means of diagnosis is discussed.

Pseudocyst formation represents a common complication of pancreatitis. Presenting manifestations are protean, and many unusual locations have been reported.[1-3] Mediastinal pseudocysts are, however, rare and only 19 such cases have appeared in the English literature since Edelin's report in 1951.[3-17] In past years, the diagnosis had rarely been made prior to surgery. The availability of gray-scale ultrasound has, however, made reliable preoperative diagnosis possible. We present an unusual presentation of a patient with a mediastinal pseudocyst in whom the diagnosis was made preoperatively.

## CASE REPORT

A 63-year old retired mobile home salesman presented with a six-month history of solid dysphagia accompanied by a 13.5 kg. weight loss. There was no odynophagia. On occasion there would be regurgitation of undigested material. Most often, however, he would be able to wash down his food by drinking large volumes of water. There was no history of heartburn or symptoms of acid reflux.

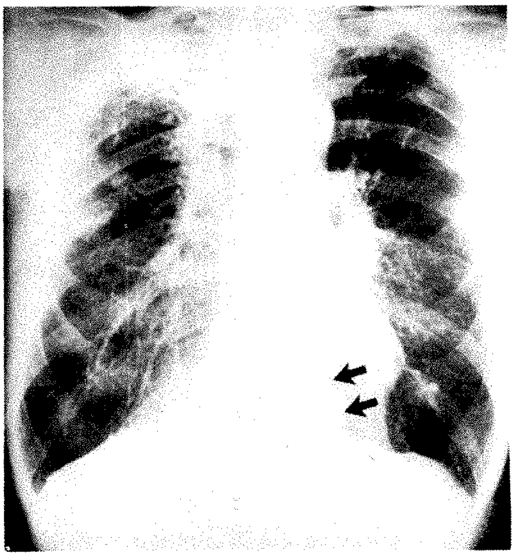

Fig. 1—PA chest showing lower mass behind the heart (arrows). Old tuberculosis is noted in right apex.

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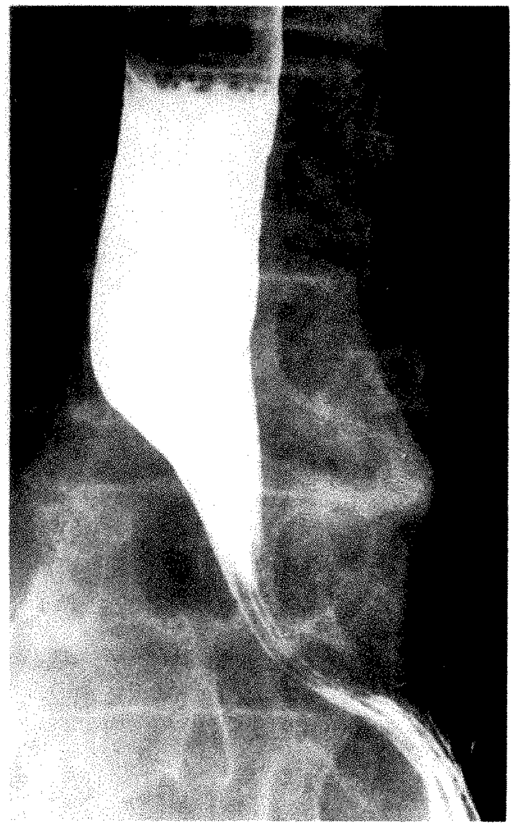

Fig. 2—Distal esophagus showing extrinsic pressure.

He denied nocturnal regurgitation of food or saliva. There was a chronic cough and a 50-pack per year history of cigarette smoking but no history of pneumonia.

He admitted to a history of chronic alcoholism and has had numerous episodes of abdominal pain and vomiting. There was one episode of documented pancreatitis in 1975.

Physical examination revealed an alert, comfortable and pleasant man. He was afebrile and normotensive. There was no icterus. Positive findings included dullness to percussion and tubular breath sounds in the right base. There was an ill-defined superficial abdominal mass with a cystic quality. The mass moved with respiration and filled the epigastrium and right upper quadrant. Laboratory evaluation included a hemoglobin of 14.4 gm.%; WBC, count of 8,300, with normal differential, normal prothrombin time and normal electrolytes and BUN. Serum transaminases and bilirubin were normal. Alkaline phosphatase was 115 I.U. (normal 85). Serum amylase was 100 U./dl. Chest x-ray revealed a mediastinal mass (Fig. 1). Oral cholecystogram did not visualize the gallbladder. Barium swallow and upper gastrointestinal series revealed a retrogastric mass and smooth, extrinsic compression of the esophagus (Fig. 2). Ultrasound examination revealed a huge pseudocyst arising in the tail of the pancreas and extending to the mediastinum (Figs. 3, 4 and 5).

Esophagogastroscopy revealed extrinsic compression of the distal esophagus. The stomach was entered without difficulty and no lesions of the cardia were seen.

Because of these findings, the patient underwent exploratory laparotomy with the preoperative diagnosis of mediastinal pancreatic pseudocyst. This finding was confirmed and cystgastrostomy and cholecystectomy were performed without difficulty. The patient made an uneventful recovery.

Six months after surgery the patient has regained his weight and no longer complains of dysphagia.

## COMMENT

Pancreatic pseudocysts dissecting into the mediastinum have been reported to cause dysphagia in only three previous cases.[10, 11, 13] More typical presenting complaints include chest pain[5, 7, 11, 14, 15] or shortness of breath.[4, 5, 7, 11, 12, 14-16] Symptoms suggestive of congestive heart failure including paroxysmal nocturnal dyspnea, orthopnea and exertional dyspnea have also been reported.[16]

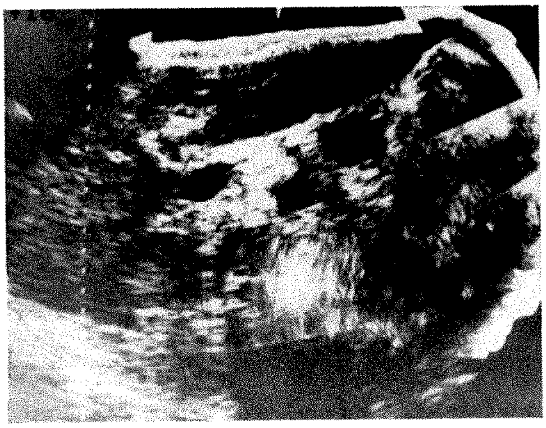

Fig. 3a

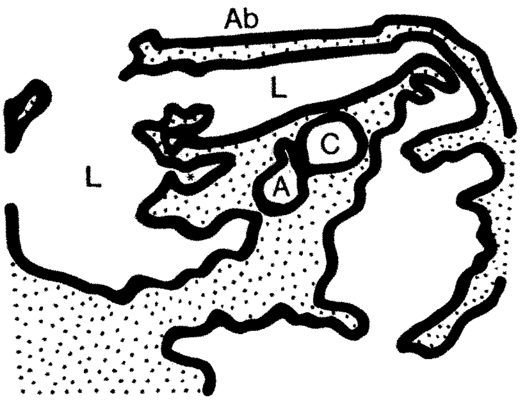

Fig. 3b

Fig. 3a—Transverse ultrasonogram showing pseudocyst arising from tail of pancreas.
Fig. 3b—Diagram of corresponding ultrasonogram. Ab = Anterior abdominal wall; L = Liver; C = Cyst; A = Aorta.

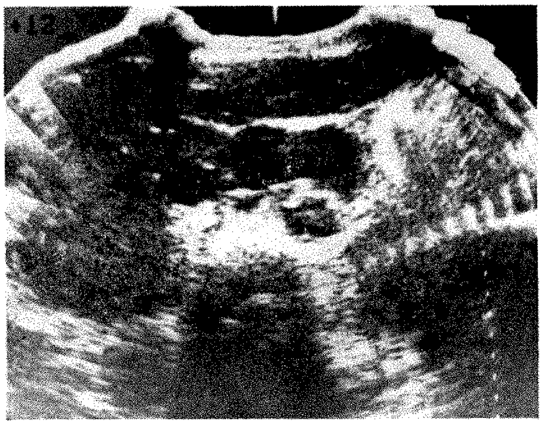

Fig. 4a

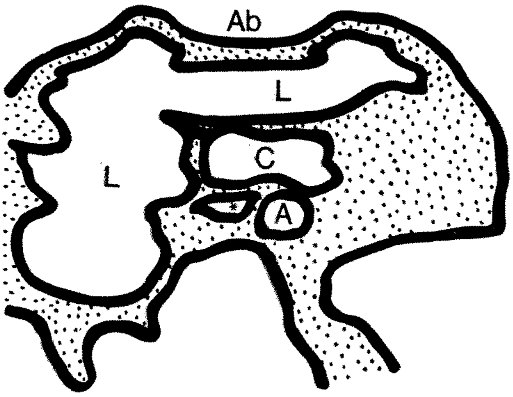

Fig. 4b

Fig. 4a—Transverse ultrasonogram performed 2 cm. cephalad to Figure 3a showing enlarging pseudocyst.
Fig. 4b—Diagram of corresponding ultrasonogram. Ab = Anterior abdominal wall; L = Liver; C = Cyst; A = Aorta; * = Inferior vena cava.

Most patients with pseudocysts have a history of recurrent pancreatitis frequently associated with alcoholism. The physical findings are usually minimal, although abdominal masses have been palpated in a minority of cases.

Chest radiographs usually demonstrate an abnormal mediastinal shadow.[4, 5, 7-9, 11, 14] Upper gastrointestinal series may show anterior displacement of the stomach and esophagus.[7, 13, 16]

Ultrasonic demonstration of pancreatic pseudocysts is well documented.[17, 18] Ultrasonic evaluation of mediastinal extension of a pseudocyst has, however, only been reported on two previous occasions.[16, 17] In one case, Kirshner, et al[16] reported therapeutic, percutaneous aspira-

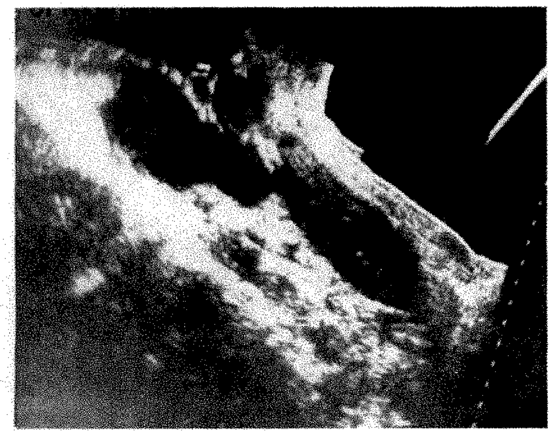

Fig. 5a

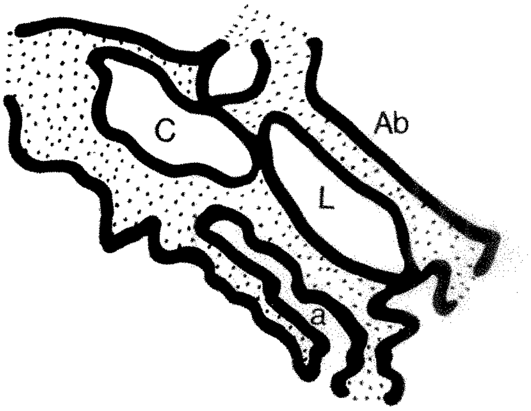

Fig. 5b

Fig. 5a—Erect longitudinal ultrasonogram showing dissection of pseudocyst into the mediastinum.
Fig. 5b—Diagram of corresponding ultrasonogram. Ab = Anterior abdominal wall; L = Liver; C = Cyst; A = Aorta.

tion of such a mediastinal pseudocyst, in which the amylase concentration of the cyst fluid was 8,885 U./dl. More conventional management consists of internal drainage of such lesions.

Although the pancreas occupies a retroperitoneal location it is seen as an abdominal structure which lies anterior to the aorta and inferior vena cava about 8 cm. cephalad to the umbilicus. The normal pancreas can be visualized with ultrasound in most patients. In fact, Haber, et al report that they can visualize the head and body in 89% of normal subjects.[19] Pancreatic pseudocysts, however, are even easier to demonstrate with ultrasound because of their characteristic sonolucent (cystic) pattern which allows easy separation from surrounding abdominal structures. Leopold has reported a 100% accuracy in detecting 13 pseudocysts with ultrasound.[18]

Because of this typical sonolucent appearance the fluid filled pseudocyst, with its strong back wall, can be easily identified from its point of origin in the pancreas to various unusual locations. Serial ultrasonograms can be obtained at 1 cm. intervals both transversely and longitudinally which allow further delineation of its exact location.

## Summary

This report describes an unusual presentation of a pancreatic pseudocyst dissecting into the mediastinum, and confirms the value of gray-scale ultrasound in providing a readily available, reliable and noninvasive means of diagnosis.

## Acknowledgment

We would like to thank Dr. Gordon McLean for his excellent diagrams which accompany the ultrasonograms.

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contents are necessary to maintain the structural and functional integrity of the normal small bowel.

Recovery of exocrine pancreatic function in protein calorie malnutrition has been noted to occur as early as two weeks after institution of a high protein diet.[13] The rapid and complete regeneration of the jejunal mucosa in our patient suggests that the elimination of alcohol, food adequate in protein, calories and vitamins and pancreatic replacement therapy, all acted in concert to achieve a normal absorptive surface where none had existed on admission.

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***Clinical Vignette***

# Isolated Granulomatous Gastritis

## REPORT OF A CASE SIMULATING GASTRIC CARCINOMA

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### INTRODUCTION

Isolated granulomatous gastritis is a rare disease. In 1963 Fahimi and his associates well established it as a distinct clinicopathologic entity separate from the gastric involvement seen in disseminated sarcoidosis and regional enteritis. Recently a case of isolated granulomatous gastritis was encountered which posed a diagnostic and therapeutic difficulty.

### CASE REPORT

A 64-year old white female was apparently in good health until approximately four and one-half months prior to her admission to Boca Raton Community Hospital when she began to experience intermittent epigastric pain. This was associated with vomiting one-half to one and one-half hours after eating and resulted in a 15.75 kg. weight loss. The patient did not experience diarrhea or constipation. She had no melena.

Past medical history revealed that the patient had epilepsy and since three years of age had been treated by 300 mg. Dilantin a day. The patient would occasionally use Trilafon for depression. Fractured hips, partial hysterectomy and appendectomy were her only previous surgical experiences. She denied smoking, alcoholic imbibing and allergies.

Physical examination revealed a thin, middle-aged female with obvious weight loss. Abdominal examination failed to reveal any mass or organomegaly. Rectal and pelvic examinations were normal.

Routine admission laboratory tests showed hemoglobin of 11.4 gm.; hematocrit of 34.4%; WBC of 5,900 and esinophils, 3%. Electrolytes were within normal limits. Chemistry profile showed slight hypocalcemia of 7.9 mg.% (normal 8.2-10.4 mg.%). Serum protein electrophoresis showed decreased gamma globulin of 0.65 gm.% (normal 0.75-1.50 gm.%); albumin, 2.75 gm.% (normal 3.47-5.62 gm.%) and total protein, 4.7 gm.% (normal 6.3-8 gm.%). Urinalysis was within normal limits. Stool was negative for blood. VDRL was nonreactive. Chest x-ray was normal. ECG was within normal limits. Barium enema and small bowel series were negative as well as proctoscopy.

An upper gastrointestinal series revealed severe gastritis, gastric hypotonicity

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From Department of Pathology and Surgery, Boca Raton Community Hospital, Inc.

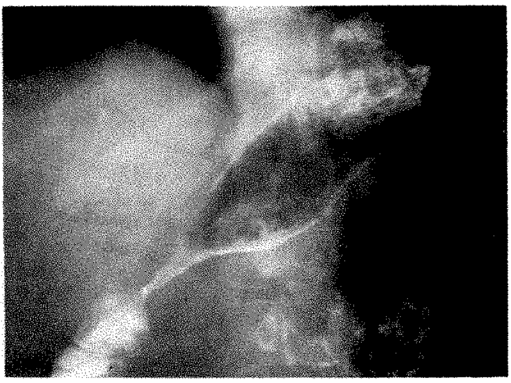

Fig. 1—Stricture of antral portion of stomach. There is no identifiable mucosal pattern or peristalsis.

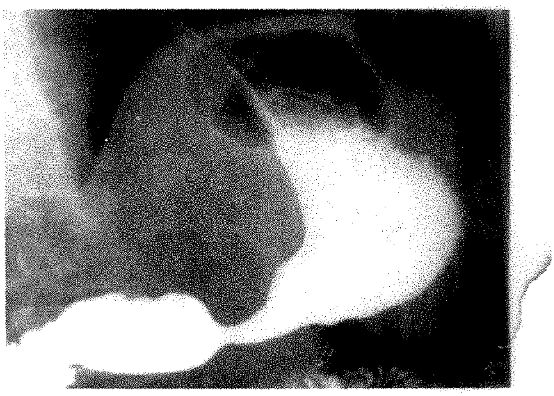

Fig. 2—Air contrast view of the stricture of the body of stomach.

and a segment of proximal antrum of the stomach with limited distensibility and a low grade functional obstruction (Figs. 1 and 2). These findings were suspicious of gastric carcinoma of linitis plastica type. No ulcer was noted. Gastroscopy showed very severe atrophic gastritis and complete lack of peristalic wave in the distal third of the stomach. No gastric or pyloric, or duodenal ulcer was noted. Gastric mucosal biopsy revealed a granulomatous gastritis of undetermined etiology. Bone marrow was negative for granuloma. Because of suspicion of carcinoma, exploratory laparotomy was performed. No abnormalities were identified at surgery except for thickened gastric wall of the distal third of the stomach and thorough examination of large and small bowel failed to reveal any evidence of Crohn's disease or other abnormality. A full thickness gastric wall segment and liver biopsy were performed for histological study. Gastric analysis demonstrated no acid, the pH was 7.8 and no response to histamine stimulation; the pH remained 7.8 in six specimens. Intermediate tuberculin and histoplasmin skin tests were negative. Sequential examination of the Kveim skin test remained negative for six months.

The patient's postoperative course was uneventful. In spite of no active treatment the patient had continued to eat well with no return of her initial symptoms over 18 months.

## MICROSCOPIC FINDINGS

The submitted fragments of stomach tissue measured 1.5 × 1.0 cm. and 0.8 × 0.6 cm. The stomach tissue exhibited multiple noncaseating granulomas which involved the mucosa, submucosa and *muscularis* (Fig. 3). The granulomas contained crystalline material in the giant cells mostly in the mucosa and submucosa, occasionally in the *muscularis* (Fig. 4). Both foreign body and Langhans' giant cells were present and epithelioid cells were prominent. These granulomas, especially in the mucosa and upper part of the submucosa, showed an outer dense zone of lymphocytes (Fig. 5). The mucosa was also infiltrated by a mixture of plasma cells, eosinophils and neutrophils. The submucosa showed fibrosis and thickening. PAS and Ziehl Neelsen stains were negative for fungi and acid fast bacilli. A liver biopsy showed fibrosis and chronic inflammation in the portal areas but no granulomas were observed. Ten of the granulomas in the mucosa and submucosa were analyzed by energy dispersive

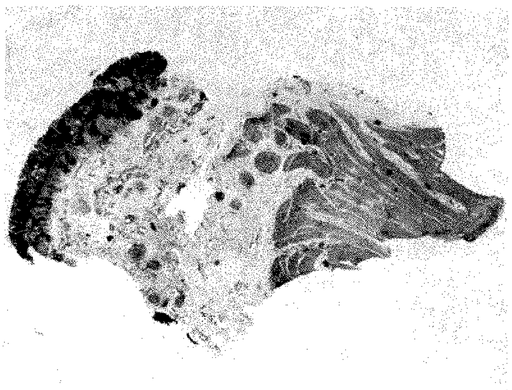

Fig. 3—Noncaseating granulomas involving the mucosa, submucosa and *muscularis* (Original magnification x7).

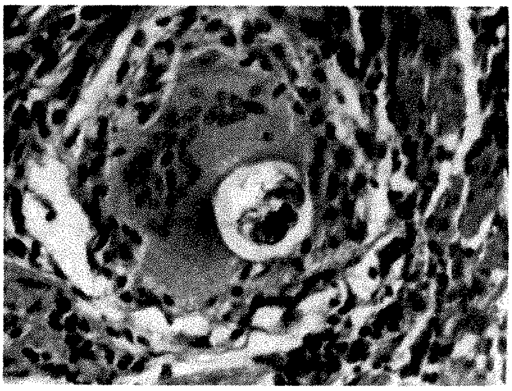

Fig. 4—Foreign body giant cell containing crystalline material (Original magnification x470).

x-ray spectrometry. Most of them contained no detectable elements other than the usual phosphorus, sulfur, potassium and calcium components of the tissue. Three of them, however, contained rather significant amounts of Mg, Al, and Si (Fig. 6). A single granuloma contained manganese (Mn).

X-ray energy spectrometry (XES) is a method for precise determination of element content. All elements from sodium through uranium are detected simultaneously by analysis of x-ray energies emitted after bombardment of the specimen by primary electrons from a high voltage source. Thus, a biological sample can be visualized in a scanning or transmission electron microscope by conventional electron optics and the resulting x-ray analyzed from the specific region being imaged. Spatial resolution of x-ray detection approaches 0.10 microns in the scanning mode and better than 0.01 microns in the transmission mode. XES is a nondestructive method which is best suited for rapid qualitative analysis of small particles *in situ* in biologic samples.

## COMMENT

Prior to the establishment of isolated granulomatous gastritis as a distinct clinicopathologic entity, several reports in the medical literature of isolated noncasetaing granulomatous inflammation of the stomach were regarded as solitary Boeck's sarcoid involvement of the stomach.[1-4]

There are two recent reports of cases which the authors regarded as gastric sarcoidosis.[5, 6] Only one patient was skin tested with Kveim antigen.[6] The patient was Kveim negative. Other authors preferred to describe their cases of isolated noncaseating granulomatous inflammation of the stomach as "sarcoid-like granulomas of the stomach",[7, 8] implying probable solitary Boeck's sarcoid involvement of the stomach. Goldgraber, et al's study of four patients reported as "nonspecific granulomatous disease" of the stomach but the authors regarded one of their cases to be regional enteritis involvement of the stomach, one case as part of eosinophilic granuloma syndrome and two cases of undetermined etiology.[9] Sherman and Moran's study of six patients regarded the granulomatous gastritis as a result of foreign body reaction to vegetable material and degenerated smooth muscle and fibrous tissue of the gastric wall.[10] An additional report of Boivin and Berry demonstrated a patient who had taken reserpine orally for many years who developed granulomatous gastri-

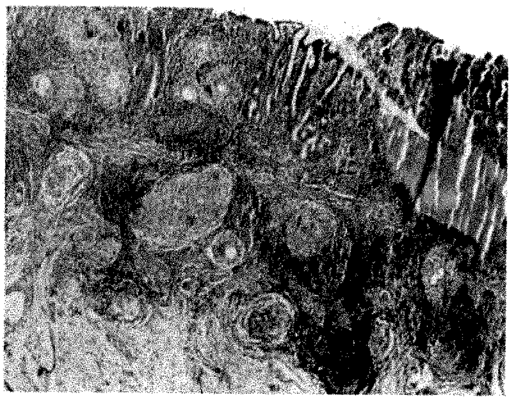

Fig. 5—Granulomas composed of epithelioid histiocytes, giant cells and outer zone of lymphocytes. Vacuolation in the giant cells is also seen (Original magnification x48).

tis.[11] The gastritis was described as a hypersensitivity manifestation to the drug. It was not until 1963 that Fahimi and his associates did an extensive review of literature to establish that isolated granulomatous gastritis was a distinct clinicopathologic entity, separate from sarcoidosis, and regional enteritis involvement of the stomach.

This clinical presentation of a patient with intermittent epigastric pain, postprandial vomiting, excessive weight loss and radiologic findings of limited distensibility and functional obstruction of the antrum certainly warranted a strong clinical suspicion of gastric carcinoma. Fahimi and his associates[12] reviewed 29 cases in addition to three of their own cases of isolated granulomatous gastritis and found that 83, 66 and 66% of patients presented with abdominal pain, weight loss and vomiting respectively. Radiologically 70% of these patients had antral or pyloric narrowing, 7% rigidity of most of the stomach and 23% had gastric ulcer.

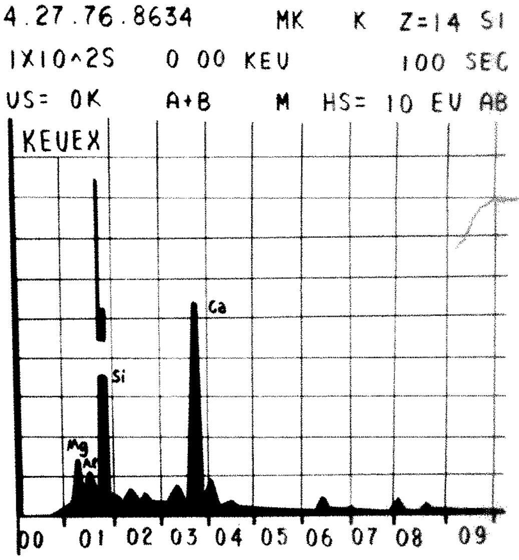

Fig. 6—Significant amounts of magnesium (Mg), aluminum (Al) and silicon (Si) in three granulomas.

The pathologic finding of discrete, nonconfluent granulomas in the mucosa, submucosa and *muscularis* in the stomach biopsy presented us with three diagnostic possibilities. 1. Infectious agents, such as tuberculosis, fungal; 2. noninfectious diseases such as sarcoidosis, regional enteritis and sarcoid-like granulomas; 3. foreign body-induced granulomatous formations such as due to talcum, aluminum silicate and beryllium. Infectious etiology of these granulomas was highly unlikely on the basis of negative acid fast and fungal stains in biopsies, a negative chest x-ray, and negative sputum cultures for acid fast bacilli and fungus. Also the patient had negative intermediate tuberculin and histoplasmin skin reactions. Disseminated sarcoidosis with gastric involvement could be ruled out because of her negative chest x-ray, negative Kveim skin reaction, absence of lymphadenopathy and liver involvement. Regional enteritis with gastric involvement and sarcoid-like granulomas associated with gastric carcinoma were unlikely as she has had no evidence of regional enteritis and gastric carcinoma in barium enema, small bowel series and proctoscopy.

The analysis of gastric biopsy by energy dispersive x-ray spectrometry shows only one-third of the granulomas contain significant amounts of Mg, Al and Si. It is difficult to ascribe any significance to these findings because there are no existing data that describe the elemental content of normal connective tissue elements of stomach or any other organ for that matter. Dust containing macrophages certainly could have sequestered in the stomach but cause and effect cannot be established. Not only has our patient a negative history of chronic beryllium poisoning and medications containing Kaolin (aluminum silicates) but also the presence of deep seated granulomas in our case is against foreign body-type of reaction. A vast search for Dilantin as being the causative agent shows that this drug so far has never been reported to cause granulomatous gastritis.

By exclusion of other possible etiologic agents, the conclusion was reached that this patient represents an individual with isolated granulomatous gastritis. We would like to convey our feeling that whenever a patient presents with upper gastrointestinal tract symptoms and x-rays suspicious of carcinoma of the stomach, isolated granulomatous gastritis should be included in differential diagnosis.

## ACKNOWLEDGMENTS

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# The Pediatric Corner

## LIPOPROTEIN-X AND OTHER TESTS IN THE DIAGNOSIS OF OBSTRUCTIVE JAUNDICE IN THE INFANT*

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The infant with elevated direct-reacting bilirubin levels requires an early specific diagnosis to identify those who would require early surgical intervention and those in whom the bilirubin levels will eventually return to normal. This study compares the accuracy of three tests: the serum lipoprotein-X (LP-X), the $I^{131}$ rose bengal (IRB) excretion and the serum alpha-fetoprotein (AFP) in making a specific diagnosis in 15 patients. When used individually the accuracy of the tests varies from 56-100%. The LP-X and IRB excretion are more specific and when in agreement are 100% accurate in the diagnosis of the neonatal hepatitis syndrome (NHS) or extrahepatic biliary obstruction (EHBO). This study suggests that both the LP-X and IRB excretion should be used in the investigation of the infant with conjugated hyperbilirubinemia.

Conjugated hyperbilirubinemia in the infant is a frequent problem encountered by the pediatrician. Several reviews[1-4] have stressed the importance of an early specific diagnosis to identify those infants with hepatocellular disease, such as the neonatal hepatitis syndrome (NHS), which does not require surgical intervention and the infant with extrahepatic biliary obstruction (EHBO) usually biliary atresia, which would require surgical correction if at all possible.

The following etiologies of conjugated hyperbilirubinemia should be considered when dealing with an infant with elevated direct-reacting bilirubin:

*Infection,* either acute or chronic will be found as the etiologic factor in about 25% of cases. Cultures, immunoglobulins, VDRL and specific serum titers for TORCH antibodies can establish the diagnosis.

*Metabolic liver disorders probably* account for another 20% of the cases. A family history, serum assays for specific enzymes, sweat electrolytes, plasma and urine

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TABLE I

INTERPRETATION OF TESTS RESULTS

| Test | Neonatal hepatitis syndrome | Extrahepatic biliary obstruction |
|---|---|---|
| Serum lipoprotein-X | Absent or if present decreasing after cholestyramine | Present and increasing after cholestyramine |
| Rose bengal excretion during cholestyramine | | |
| Stool | Greater than 10% | Greater than 10% |
| Scintiphoto | Partial excretion, activity in the intestinal tract at 4 and 24 hours | No excretion, no visible activity in the intestinal tract at any time |
| Serum alpha-fetoprotein | Greater than 4 mg./dl. | Less than 4 mg./dl. |

TABLE II

LIPOPROTEIN-X, ROSE BENGAL EXCRETION, AND ALPHA-FETOPROTEIN IN NEONATAL HEPATITIS SYNDROME

| Case | Lipoprotein-X mg./dl. | | Rose bengal excretion % or scintiphoto on cholestyramine | AFP mg./dl. |
|---|---|---|---|---|
| | Pre-CSM | Post-CSM | | |
| 1 | 263 | 313* | 12.1 | 12 |
| 2 | 154 | 80 | 18.2 | 2* |
| 3 | 120 | 12 | Partial excretion | 6 |
| 4 | 84 | 52 | 11.4 | 2* |
| 5 | 84 | 0 | 1.6* | 6 |
| 6 | 63 | 30 | 13.2 | 5 |
| 7 | 34 | 8 | 64.0 | 4* |
| 8 | 0 | 0 | 5.8* | 16 |
| 9 | 0 | 0 | Partial excretion | 4* |

* False positive.

aminograms and chromatography will aid in the diagnosis of these disorders. Alpha$_1$ antitrypsin deficiency is frequently diagnosed now and this enzyme level should always be determined in all infants with conjugated hyperbilirubinemia. Liver damage due to parenteral nutrition should be included in this group. The diagnosis can be established by discontinuation of the parenteral nutrition and noting a return of the bilirubin to normal values.

*Hematologic disorders:*—Hemolytic anemia in the newborn and infant may be associated with conjugated hyperbilirubinemia.

*Hepatocellular disease or extrahepatic biliary obstruction:*—The majority of infants with elevated direct-reacting bilirubin will be found in this group. Familial disorders such as fatal intrahepatic cholestasis (Byler's Disease) and conjugating disorders may be diagnosed by history or biopsy. The diagnostic dilemma for the physician is the differentiation of the infant with NHS or EHBO. Numerous tests are reported to differentiate between these two groups but none of these tests are absolutely diagnostic. Laparotomy, liver biopsy and operative cholangiogram is probably the most accurate diagnostic test. Not every patient should be subjected to the latter procedures. Thus we are always looking for more specific and accurate diagnostic tests.

It has been observed that in patients with hepatocellular disease and EHBO, physiologic cholestasis, a reduction in bile flow, occurs. This is evidenced by elevated serum bile acid and is usually accompanied by hyperbilirubinemia. In the neonatal period or early infancy, pruritus does not accompany cholestasis. No other laboratory screening procedure has detected cholesta-

TABLE III

LIPOPROTEIN-X, ROSE BENGAL EXCRETION AND ALPHA-FETOPROTEIN IN EXTRAHEPATIC BILIARY OBSTRUCTION

| Case | DX | Lipoprotein-X mg./dl. | | Rose bengal stool excretion % or scintiphoto on cholestyramine | AFP mg./dl. |
|---|---|---|---|---|---|
| | | Pre-CSM | Post-CSM | | |
| 1 | B.A. | 709 | 790 | 3.4 | 4 |
| 2 | B.A. | 647 | 800 | 6.4 | 12* |
| | B.A. | 438 | 313* | 3.3 | 2 |
| 4 | B.A. | 200 | 300 | No excretion | 2 |
| 5 | B.A. | 52 | 120 | No excretion | 6* |
| 6 | C.C. | 63 | 104 | 9.5 | 1 |

B.A. = Biliary atresia; C.C. = Choledochal cyst.
* False negative.

sis in infants, so that a high direct-reacting bilirubin level is usually the first suggestion of this problem.

Russ, et al[5] demonstrated the presence of an increased lipoprotein in the serum of a patient with biliary cirrhosis. Seidel, et al[6] found this macromolecule in the serum of patients with obstructive jaundice and called this lipoprotein-X (LP-X).

Poley, et al[7] reported the presence of LP-X in the serum of infants with cholestatic liver disease if there was no evidence of severe hepatic decompensation. This group used the presence of LP-X in the serum to diagnose EHBO obstruction.[8] Campbell, et al[4] reported quantitative decreases in the serum LP-X after a course of cholestyramine (CSM) given for 10-20 days in infants with conjugated hyperbilirubinemia when there is a potentially patent biliary system. This group also reported greater specificity of the $I^{131}$ rose bengal (IRB) stool excretion between infants with neonatal hepatitis syndrome and EHBO during a course of CSM.[7]

Zeltzer, et al[9] found the measurement of serum alpha-fetoprotein (AFP) useful in the differentiation between NHS and EHBO. Andres, et al[10] found significant overlap of the serum AFP in the NHS and EHBO but higher serum AFP levels were present in infants with NHS than in the ones with EHBO.

This study was designed to compare the accuracy of the quantitative serum LP-X before and after CSM, IRB excretion test (stool or scintiphoto) during the course of CSM, and the serum AFP in the diagnosis of conjugated hyperbilirubinemia in infants.

## MATERIAL AND METHODS

Fifteen infants from one to two and half months of age with conjugated hyperbilirubinemia after exclusion of infectious, metabolic or hematologic etiologies, were identified. In all it was necessary to decide whether a surgical procedure should be done or not. The direct-reacting bilirubin level was greater than 3 mg./dl. or greater than 40% of the total bilirubin at the time of entry into the study group.

The following protocol was followed for each patient:

TABLE IV

DIAGNOSTIC ACCURACY OF TESTING PROCEDURES IN 15 PATIENTS

| Diagnosis (N) | LP-X | Rose bengal | Feto prot. |
|---|---|---|---|
| Neonatal hepatitis syndrome (9) | 8/9 (89) | 7/9 (78) | 5/9 (56) |
| Extrahepatic bile duct obstruction (6) | 5/6 (83) | 6/6 (100) | 4/6 (67) |

Figures in parentheses are percentages.

TABLE V

DIAGNOSTIC ACCURACY WHEN BOTH LIPOPROTEIN-X AND ROSE BENGAL EXCRETION ARE IN AGREEMENT

| Diagnosis | Lipoprotein-X and rose bengal |
|---|---|
| Neonatal hepatitis syndrome | 6/6 (100) |
| Extrahepatic biliary obstruction | 5/5 (100) |

Figures in parentheses are percentages.

In 15 patients studied both tests were in agreement in 11 patients only.

1. Documentation of several elevated direct-reacting bilirubin levels. 2. Obtain two separate fasting blood specimens for quantitative serum LP-X by agar gel electrophoresis and microphosphate determinations.[11] 3. Obtain serum for AFP level by the Ouchterlony double diffusion technic. (Bio-Science Laboratories, Rockville Centre, NY). 4. Give CSM, 4 gm./day in divided doses mixed with regular formula. 5. Obtain fasting serum for quantitative LP-X on the 10th day of CSM intake. 6. Perform an IRB excretion test with scintiphoto at four and 24 hours or stool collection for 96 hours. At the completion of this period discontinue CSM. 7. A laparotomy, liver biopsy and operative cholangiogram are performed when indicated and also to confirm the diagnosis.

## RESULTS

The tests were interpreted as shown in Table I.

Nine infants were identified and discharged with the final diagnosis of NHS. The first three patients investigated had laparotomies, liver biopsies and operative cholangiograms identifying patent extrahepatic biliary systems. The biopsies confirmed the diagnosis of hepatitis syndrome. Further experience with the accuracy of the tests enabled us to avoid a surgical procedure in the latter six patients. All nine patients have been followed. The serum bilirubin and other liver function tests have returned to normal. The quantitative LP-X pre- and post-CSM, the IRB excretion test during the CSM therapy and the serum AFP are indicated in Table II. Note the false positive results.

Six patients had EHBO, confirmed by laparotomy, liver biopsy and operative cholangiogram. When the diagnosis was made at laparotomy corrective surgery was done. Hepatoportoenterostomy was done in the five patients with biliary atresia and resection of the choledochal cyst in one patient. Three patients with hepatoportoenterostomies have expired, two are alive as of now but have evidence of hepatic decompensation. The patient with the choledochal cyst is growing well and has a normal serum bilirubin level and liver function tests. The results of the tests performed are shown in Table III. Note the false negative results.

The diagnostic accuracy for the tests in the 15 patients is indicated in Table IV.

Only in the patients with EHBO is the IRB excretion test during CSM therapy always correct. Of the 15 patients investigated and diagnosed by the three tests, in only 11 was there agreement of the LP-X and IRB excretion (Table V). The AFP had too many false positive and negatives to use as a diagnostic test and is therefore not included in this comparison.

## COMMENT

In the infant with conjugated hyperbilirubinemia many tests have been advocated to reliably distinguish between the infant with NHS and those with EHBO.[1-4] All reviews indicate that none of these tests is completely accurate. Physicians are continually searching for more specific diagnostic tests as one would not subject every patient to a closed or open liver biopsy. It also is important to identify those patients in whom corrective surgery should be attempted.

Campbell, et al[8] have reported that the quantitative serum LP-X before and after CSM is the most accurate test (96.4%) in identifying the infant with EHBO. The present study suggests that the LP-X test may not always be correct. A combination of the LP-X test with CSM and the IRB excretion test during CSM when in agremeent, will always be correct. We do not find the AFP of any diagnostic value and do not recommend its use.

Javitt, et al[12] have not found that serum bile acid values could differentiate between the neonatal hepatitis syndrome and extrahepatic biliary atresia. Elevated serum bile acids will only establish the diagnosis of cholestasis.

We would recommend that the serum LP-X before and after CSM be used in conjunction with the IRB excretion test for investigation of the infant with conjugated hyperbilirubinemia. If LP-X cannot be demonstrated in the serum of the infant on two occasions, we would observe the patient without surgical exploration. If the result of the LP-X pre- and post-CSM is equivocal but the IRB excretion test suggests EHBO, the infant would have a surgical procedure performed to establish the final diagnosis. If the LP-X test pre- and post-CSM as well as the IRB excretion test during CSM suggests EHBO, the infant will have a laparotomy, liver biopsy and operative cholangiogram. If these confirm the diagnosis of EHBO a shunt procedure will be done even though this may only be successful in 10-20% of the patients.[13,14]

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# State of the Art*

## INTESTINAL MOTILITY: CURRENT CONCEPTS

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There has been remarkable improvement in our understanding of the control mechanisms of gastrointestinal motor activity during the past decade. Although much knowledge has been acquired concerning esophageal motor function and gastric emptying, relatively less attention has been paid to intestinal motility. This review focuses on the control mechanisms of small bowel and colon motor activity, with a brief discussion of the major motor disorders of these portions of the gastrointestinal tract.

### MOTILITY OF THE SMALL BOWEL

Mixing and propulsion[1] are the two major roles of motor activity in the small intestine. Two kinds of intestinal motor activity serve to achieve these: First, *segmentation* or stationary ring contractions that efficiently mix the internal content of the small intestine and second, *peristalsis* or moving ring contractions, which are the major propulsive movements in the small intestine. Whether segmentation has propulsive quality is unsettled.

Smooth muscle contraction in the small intestine, like the rest of the gastrointestinal tract, depends on: 1. the electrical properties of the smooth muscle membrane; 2. extrinsic innervation; 3. intrinsic innervation and 4. circulating humoral agents. The backbone of the contractions is the phasic changes in the electrical potential of muscle cell membranes known as slow waves or Electrical Control Activity (ECA). Since the electrical output of this system alternately achieves maximal and minimal values it is called an oscillator[2] and because the frequency of each oscillator is influenced by adjacent oscillators, they are called coupled oscillators. Slow waves are the main electrophysiologic property of the smooth muscle. In the small intestine their frequencies decline from duodenum to ileum, being about 12 cycles/min. in the former and about 7 cycles/min. in the latter.[2] This declining phenomenon (Alvarez gradient) has been attributed to either a single pacemaker with a Wenckebach-type rhythm, or multiple pacemakers with progressively declining internal frequency along the small bowel.[3] In hyperthyroidism the duodenal frequency of the slow waves persists to levels of 160 cm. or more from the incisors, indicating a shift of pacemaker location in this condition.[2] When the adjacent pacemakers are phase-locked (one-to-one relationship with a lag), spike bursts or potentials are generated and translated into contractions. Phase-locking in a short segment of the bowel usually results in segmentation, while in a long segment it produces a propulsive movement.[4]

Innervation of the small bowel is handled through the vagus and splanchnic nerves.[3] The *vagus* carries four different types of fibers to the small bowel: 1. preganglionic cholinergic; 2. sympathetic adrenergic fibers, which are originated from cervical ganglia; 3. nonadrenergic, noncholinergic inhibitory fibers and 4. sensory fibers that have originated from mechanoreceptors, chemoreceptors, and osmoreceptors of the small bowel. Distention of the small bowel at any point, through the mechanoreceptors, initiates contraction proximally and relaxation distally, a phenomenon known as Bayliss and Starling peristaltic reflex.[5] Three types of fibers are carried in the *splanchnic* nerves: 1. preganglionic sympathetic; 2. postganglionic sympathetic and 3. sensory fibers for pain.

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The network of the nerve fibers is organized into three plexuses; subserous plexus, myenteric plexus and submucosal plexus. Through their chemical neurotransmitters, these nerve fibers serve to increase or decrease the excitability of the muscle cell membrane. A spike potential cannot occur unless a certain level of muscular excitability has been achieved. Intrinsic neurons also provide inhibitory innervations to the circular muscle along the alimentary canal.[6] The inherent excitability of the musculature, thus, is continuously suppressed by ongoing release of an inhibitory transmitter substance from spontaneously active neurons within ganglia of the enteric plexuses. On the same basis, ileus results from overactivity of this inhibitory system rather than cholinergic excitatory nerve dysfunction. Muscarinic and nicotinic receptors on the smooth muscle both respond to acetylcholine and its analogues. Stimulation of the $\beta$-sympathetic receptor induces contraction, while $\alpha$-receptors have excitatory or inhibitory effects. Recently, a serotonin receptor has also been suggested.[7]

Of the gastrointestinal hormones, *cholecystokinin*-like peptides increase the motor activity of the small bowel.[8] The role of intravenously administered cholecystokinin on the motor activity of the small bowel is rapid and more striking than gastrin.[9] Such an increase in motor activity usually is accompanied by a corresponding decrease in small bowel transit time.[10] On the other hand, motor activity of the small bowel is decreased by *secretin*[8] and *glucagon*.[11] *Motilin* and its role on interdigestive electrical activity of the human small bowel remains controversial.[12, 13] *Prostaglandins F* usually contract both circular and longitudinal muscle layers, whereas *prostaglandins E* contract the longitudinal layer and relax the circular layer.[14] *Serotonin* (5-HT) stimulates the small intestine and inhibits colon muscle fibers.[15]

## MOTOR FUNCTION OF THE SMALL BOWEL IN HEALTH AND DISEASE

*Feeding:*—Feeding habits have an important role in motor activity of the small bowel. Feeding enhances the cycles of myoelectric activity. For example, a pig eats about 40 times a day, and has almost continuous electrical activity in the small intestine. On the other hand, fasting reduces myoelectric complexes as well as motor activity. In man, after 15-18 hours of fasting, only minimal motor activity is recorded.[16] Feeding, however, has no effect on the Basal Electrical Rhythm or slow waves.

*Sleep:*—Small bowel motor activity decreases during sleep.[1]

*Idiopathic intestinal pseudo-obstruction (IIP):*—This chronic condition is characterized by recurrent obstructive symptoms without evidence of mechanical obstruction. The disorder of the gastrointestinal smooth muscle involves the esophagus,[17] stomach and small bowel[18] as well as colon. It is believed that the disease is secondary to ineffective intestinal propulsion.[19] Since a variety of factors may modify gastrointestinal propulsive function, it seems that IIP may arise from a number of different causes. Light and electron microscopic studies have recently shown marked thinning and degeneration of the smooth muscle of the small bowel.[20] Sarna and his colleagues have demonstrated hyperpolarization of intestinal smooth muscle. They suggest that this may explain the absence of electrical control activity or slow waves and most of the motor disorders seen in these patients.[21] Defective neural control system, disturbances of gastrointestinal hormone secretion and increase in inhibitory circulating substances, such as prostaglandin E,[22] have also been considered. In many cases, IIP is associated with other more familiar disorders such as amyloidosis,[23] scleroderma,[24] hypoparathyroidism[25] and Parkinson's disease.[26]

*Paralytic ileus (acute pseudo-obstruction):*—This condition has been described in association with hypokalemia,[20] myxedema,[27] congestive heart failure, pancreatitis, chronic renal failure and various infectious processes including peritonitis, pneumonia and sepsis.[28] Ileus currently is considered to be due to inhibitory neural system overactivity and is therefore often treated with adrenergic $\alpha$-receptor-blocking agents like phentolamine.[29] Furthermore, in ileus, the activity of all parts of the gut can be stimulated by an acetylcholine analogue, such as bethanechol.[30]

## COLON MOTOR ACTIVITY

Circular muscle fibers in the colon are 1 mm. wide bands divided by transverse septa. Longitudinal muscle fibers, in man and herbivores, are assorted in the three bundles known as *taenia coli.*

Two kinds of motor activity have been recorded in the colon: First, *segmental contractions* are of smaller amplitude and are shorter in duration in the ascending and transverse colon, the amplitude increases toward sigmoid colon,[31] even to the extent of blocking the lumen. The over all effects of these contractions are to produce only limited to-and-fro movement of colonic content and generate resistance to propulsion of the feces. The frequency, amplitude and duration of the independent segmental contractions vary widely from time to time in the same subject.[31, 32] Comparison of separately analyzed consecutive periods from the same subject, however, shows less variation under resting conditions.[33] Second, *mass movement* consists of very large pressure waves, lasting more than one minute at a time.[34] Radiologically their appearance is preceded by sudden disappearance of the haustral segmentation. This kind of motor activity seems to be important in transit of large quantities of stool over a considerable length of the colon.[34]

Phasic changes in electrical potential of the muscle cell membrane (slow waves), as in the stomach and small bowel, occur constantly, whether or not segmented contractions are present.[35] Each oscillator is electrically coupled to adjacent oscillators. The oscillators that are strongly coupled (phase-locked) in the stomach, however, are weakly coupled in the colon.[36] In the colon, slow waves appear at a rate of 3, 6 and 9 cycles/min. Multiple pacemakers with different internal frequencies are proposed for the colon, analogous to the phenomenon of ectopic and wandering pacemakers in the heart.[37] Contractions are the translation of spike bursts. These represent transient shifts of ions across muscle cell membrane, triggered by the slow waves when neural and humoral factors allow them to occur.

The innervation of the colonic muscle is through the *vagus erigentes* (parasympathetic) and fibers from the *hypogastric* and *celiac ganglia* (sympathetic). There appear to be two types of excitatory and two types of inhibitory nerves.[30] *Cholinergic excitatory nerves,* acetylcholine analogues and anticholinesterases increase segmental contractions. Similar observations have been made after pretreatment with anticholinergic agents. This type of response has been attributed to *noncholinergic* excitatory fibers. In the guinea pig, serotonin has been considered as the chemical neurotransmitter of the noncholinergic excitatory fibers. This, however, does not seem to be the case in man, since serotonin usually causes relaxation. Stimulation of *adrenergic inhibitory* fibers causes relaxation preventable by adrenergic antagonists. There are also, *nonadrenergic inhibitory* fibers that are not affected by adrenergic antagonists. Adenosine triphosphate (ATP) has been proposed as the possible neurotransmitter of this system.[38] Aside from $\alpha$-adrenoreceptors, the presence of dopamine receptors in the sigmoid colon has recently been suggested,[39] stimulation of either resulting in muscle contraction.

Serotonin inhibits colonic motility. This could be taken to account for its role in the diarrhea seen in carcinoid syndrome, since it has been demonstrated that motor activity actually declines in diarrheal states.[40] Cholecystokinin, when administered exogenously,[41] or released endogenously,[42] stimulates colonic motor activity. The effect of cholecystokinin, as in small bowel, is more prominent than that of gastrin.[9] On the other hand, secretin[41, 43] and glucagon[11] inhibit segmental contractions. No specific role has been established for the prostaglandins in colon motor activity.

## DISORDERS OF COLONIC MOTOR ACTIVITY

*Paradoxical motility in diarrhea and constipation:*—Segmental contractions tend to be reduced in diarrhea and increased in constipation.[40] This apparent paradox is resolved if the hypothesis regarding delay in transit produced by segmental contractions is true. Recently, a segmental area of overactivity at the rectosigmoid junction of constipated subjects has been described. This area is not influenced by either secretin or cholecystokinin but is markedly inhibited by atropine and glucagon.[44] It is not known, however, whether the increased motor activity in constipation and the decreased motor activity in diarrhea are results or causes of these conditions.

*Irritable bowel syndrome:*—Colonic motor activity is increased in patients with *spastic colon* and decreased in those with *painless diarrhea.*[45] Although this pattern is commonly observed among these patients, it has little diagnostic value. Increased colonic muscle reactivity to cholinergic agents, cholecystokinin,[46] food [47] and emotional stress is another feature of this syndrome. Furthermore, the ratio of 3-6 cycles/min. of colonic basal electrical rhythm or slow waves is increased in these patients.[48]

*Diverticular disease of the bowel:*—Colonic diverticular disease is characterized by marked thickening of the bowel muscle. It is not clear whether this anatomical abnormality alone or in combination with increased force of muscle contraction produces the high amplitude segmental contractions that lead to the extrudings.[49] Muscle abnormality seems to be the primary event, since intraluminal pressure diminishes after sigmoid myotomy.

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# The Radiology Corner*

## DUODENAL INVOLVEMENT WITH CROHN'S DISEASE: A SPECTRUM OF RADIOGRAPHIC ABNORMALITY

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The clinical and radiographic features of 22 cases of duodenal Crohn's disease were analyzed. The presenting clinical findings in the majority suggested peptic disease rather than regional enteritis. There were no cases of isolated duodenal Crohn's disease but a spectrum of radiographic abnormalities was produced by duodenal involvement with Crohn's disease which simulated a variety of clinical entities. A radiographic examination of the small bowel or colon was useful to confirm a diagnosis of Crohn's disease when duodenal abnormalities were suggestive.

Involvement of the duodenum with regional enteritis is an uncommon manifestation of Crohn's disease occurring in 0.5-7% of cases.[1-7] In over 80% of instances Crohn's disease will have involved the colon or small bowel prior to duodenal involvement with regional enteritis being detected. Rarely, however, transmural duodenal enteritis will precede or occur concomitantly with involvement of the small bowel or colon.[8, 9] An awareness of the spectrum of radiographic abnormalities regional enteritis produces in the duodenum may enable a diagnosis of Crohn's disease to be suggested even though it is not clinically suspected. We present our experience with 22 cases of duodenal enteritis and discuss the various radiographic patterns which may be produced and the disease entities which may be simulated.

### CLINICAL MATERIAL

The medical records and radiographic findings in 22 patients with duodenal enteritis were reviewed. The clinical information is summarized in Table I. Our series included 15 males and seven females aged seven to 49. A diagnosis of Crohn's disease was made by prior surgery in 13 patients and confirmed by endoscopy, biopsy and/or typical radiologic findings in the remaining nine. Sixteen patients had a known diagnosis of Crohn's disease for 2-15 years prior to duodenal involvement being identified while in five patients the diagnosis of duodenal Crohn's disease was made concomitantly with stomach, small bowel or colonic involvement.

### RADIOGRAPHIC FEATURES

Crohn's disease of the duodenum may present a spectrum of radiographic change

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TABLE I

| Case | Sex | Age | Prior surgery | Diagnosis Crohn's prior to duodenal involvement (years) | Location of radiographic abnormality |
|---|---|---|---|---|---|
| 1 | F | 25 | Yes | 2 | D1,D2 |
| 2 | M | 12 | No | 0 | D2,I,C |
| 3 | F | 22 | No | 4 | S,I,C,D1 |
| 4 | F | 49 | Yes | 15 | S,I,D1 |
| 5 | M | 7 | No | 0 | D2,I,C |
| 6 | M | 21 | Yes | 11 | D2 (prior ileostomy) |
| 7 | F | 25 | Yes | 4 | S,D1,D2 |
| 8 | F | 18 | Yes | 5 | D1,D2,I,C |
| 9 | F | 34 | No | 5 | D2,J,I |
| 10 | M | 24 | Yes | 3 | D3,D4,I,C |
| 11 | M | 23 | No | ? | D1,D2,J,I,C |
| 12 | M | 22 | No | 0 | D1,D2,I,F |
| 13 | M | 34 | Yes | 11 | D2,I |
| 14 | M | 20 | No | 0 | D2,I,C |
| 15 | M | 28 | Yes | 6 | D2,D3,D4,J,I,C,F |
| 16 | M | 29 | Yes | 4 | D2,I |
| 17 | M | 20 | No | 4 | I,C,D2 |
| 18 | M | 30 | Yes | 5 | I,C,S,D2 |
| 19 | F | 35 | Yes | 2 | D2,J,I,C |
| 20 | M | 25 | Yes | 4 | D1,D2,D3,D4,J,I,C,F, |
| 21 | M | 25 | No | 0 | D2,C |
| 22 | M | 33 | Yes | 4 | D2,J,I,C,F |

S — Stomach
J — Jejunum
I — Ileum
C — Colon
F — Fistula

D — Duodenum
  1 — Bulb
  2 — 2nd portion
  3 — 3rd portion
  4 — 4th portion

TABLE II

RADIOGRAPHIC MANIFESTATIONS OF CROHN'S DISEASE OF THE DUODENUM

1. Abnormal folds
   - A. Thickened, slightly enlarged
   - B. Nodular, blunted, markedly distorted
   - C. Loss of mucosal pattern, linear fissures, cobblestone appearance
2. Stenosis
   - A. Pseudodiverticula
   - B. Fixed strictures—may be short or long, single or multiple
   - C. Transient—associated with spasm—"string sign"
   - D. Pyloroantrum narrowing
3. Ulceration
   - A. Irregular, transverse and linear
   - B. Focal—simulating peptic ulceration
4. Perforation
   - A. Fistula—colonic, biliary, small bowel
   - B. Periduodenal abscess

(Table II). Minimal abnormalities consist of blunting and thickening of the mucosal folds (Fig. 1) which may be difficult to distinguish from duodenal edema due to peptic ulcer disease or adjacent pancreatitis. More marked involvement produces narrowing and spasm of the descending duodenum without definite mucosal destruction. In extensive involvement of the duodenum with Crohn's disease radiographic abnormalities are more pronounced. Typically there is marked thickening of the folds associated with linear ulcerations and a cobblestone appearance (Fig. 2), or areas of fixed luminal narrowing with pseudodiverticula representing focal outpouchings of relatively uninvolved duodenum adjacent to more severely involved portions of the duodenum bowel wall (Fig. 3).

The descending duodenum is the segment most commonly involved with duodenal Crohn's disease. Crohn's disease, however, may affect any portion of the duodenum and Figure 4 illustrates a case in which the second duodenum was spared with the third and fourth portion of the duodenum demonstrating nodular thickening, tubular narrowing and loss of the normal mucosal pattern. In this case, differentiation from primary duodenal malignancy is virtually impossible by radiographic criteria alone.

Stenosis of the duodenum is a common sequel of duodenal Crohn's disease. It may be secondary to a severe degree of duodenal spasm or the stenosis may be fixed and produce high grade gastric outlet obstruction (Fig. 5). While Crohn's disease generally involves a long segment of the duodenum, rarely the disease will produce a short narrowed duodenal stricture with overhanging margins and mucosal destruction which may be difficult to distinguish from primary duodenal adenocarcinoma. The findings of granulomatous disease in other segments of large or small bowel should suggest that a short stricture is inflammatory rather than neoplastic in nature.

Occasionally duodenal Crohn's disease will produce an area of thickened folds in the postbulbar segment of the duodenum with a segmental narrowing containing an ulceration (Fig. 6). Radiographic differentiation from benign postbulbar ulceration secondary to peptic disease is extremely difficult in these instances.

While fistula formation is a common manifestation of colonic or ileal Crohn's disease, fistulas secondary to Crohn's disease of the duodenum are exceedingly rare.[10] When fistulas occur they are most often duodenal colic[3] but duodenal biliary[4, 5, 11] as well as frank periduodenal abscess formation (Fig. 7) may occur as complications of duodenal Crohn's disease.

The second portion of the duodenum was the segment involved with duodenal Crohn's disease in 19 patients. The duo-

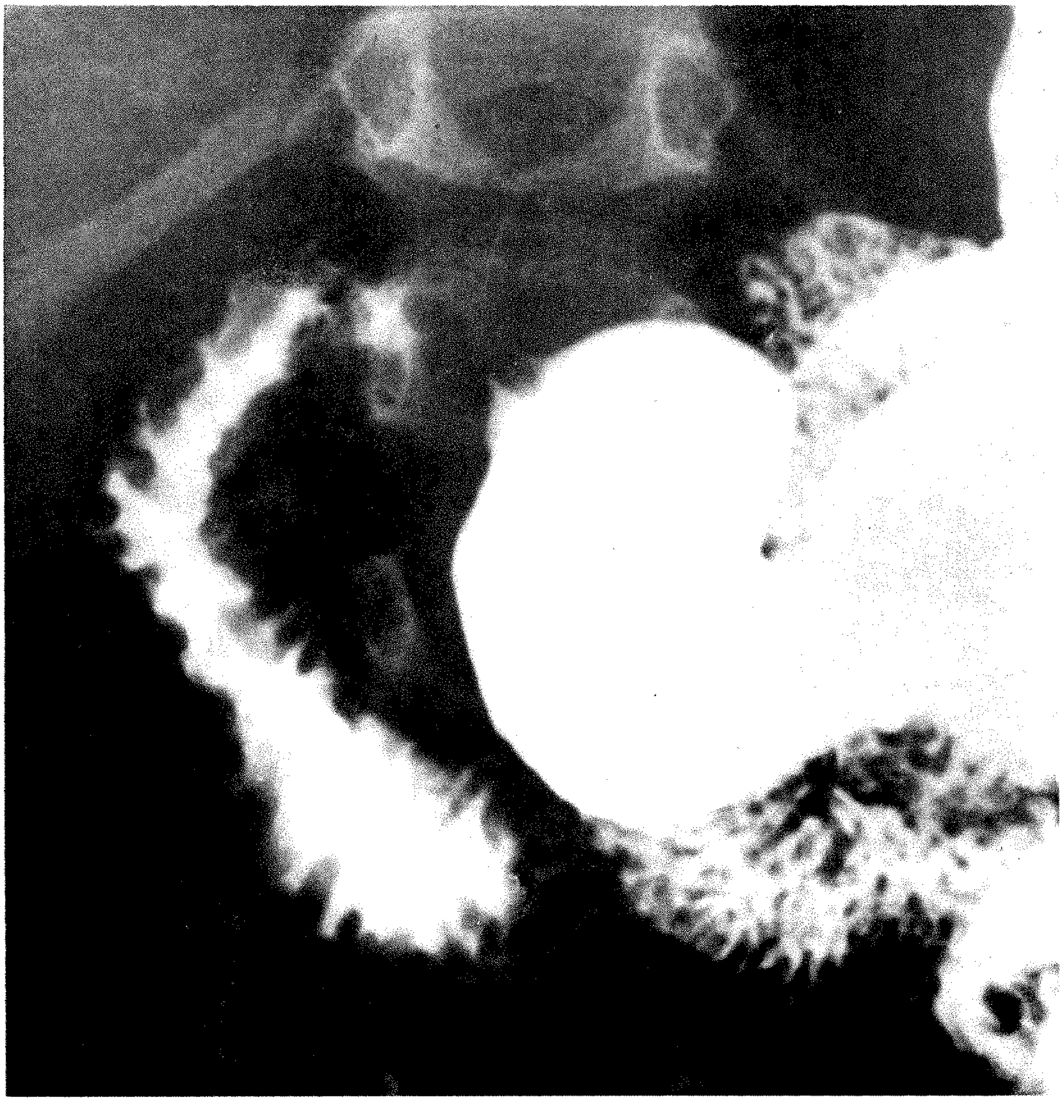

Fig. 1—Spasm of the duodenal bulb and widespread enlargement and thickening of the duodenal folds produced by Crohn's disease in a seven-year old boy. This is the youngest patient reported with duodenal involvement with Crohn's disease.

denal bulb was involved in eight patients, all of which had contiguous involvement of the stomach or second part of the duodenum. In our series there were no examples of isolated duodenal bulb involvement with Crohn's disease but one patient had Crohn's disease involving only the third and fourth portion of the duodenum.

## Comment

All of our patients with duodenal Crohn's disease had radiographic changes of Crohn's disease elsewhere in the large or small bowel at the same time or prior to the duodenal involvement with Crohn's disease being recognized. In eight cases, how-

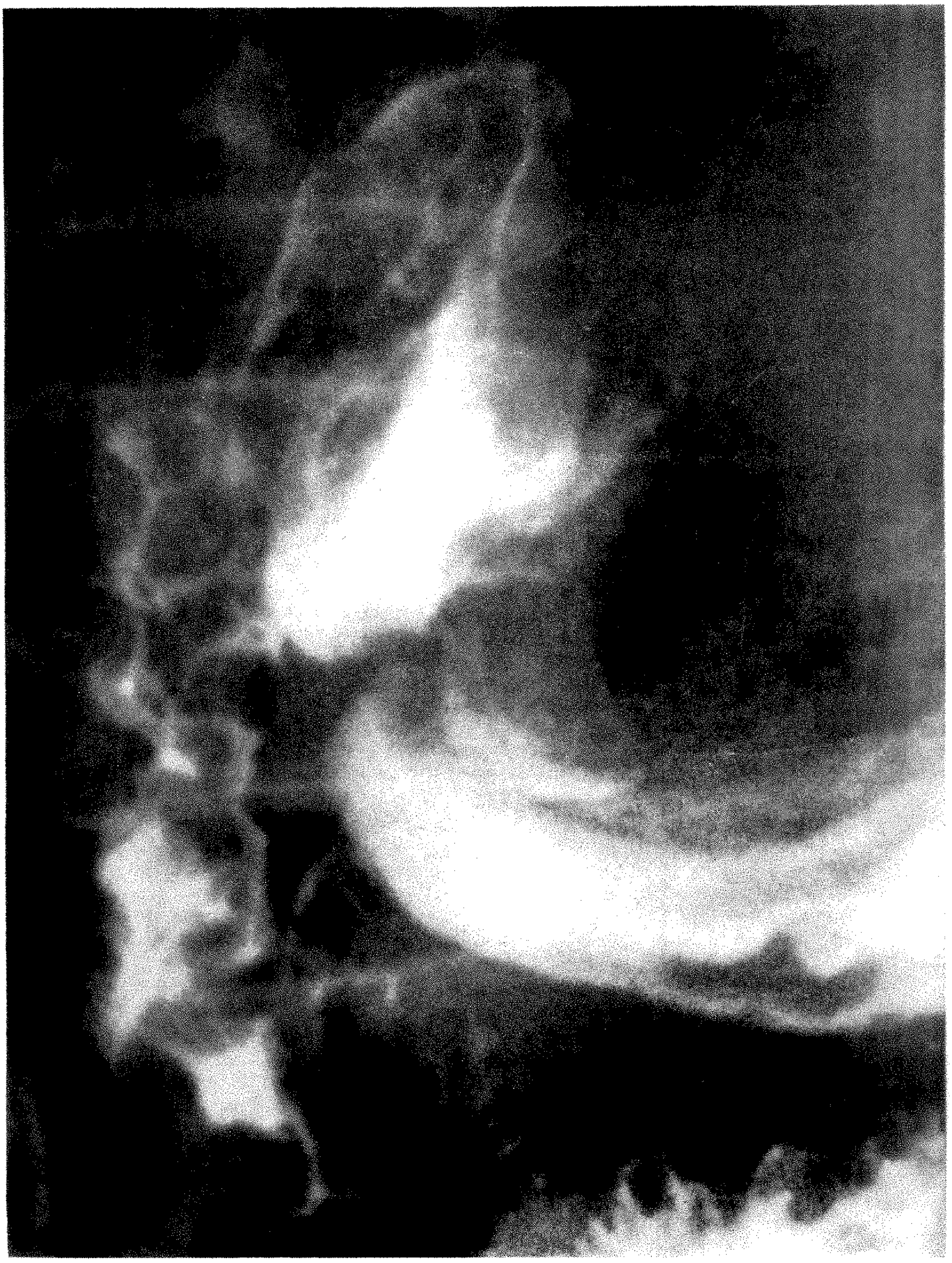

Fig. 2—A spot film of the descending duodenum reveals markedly coarsened folds and nodularity of the mucosa.

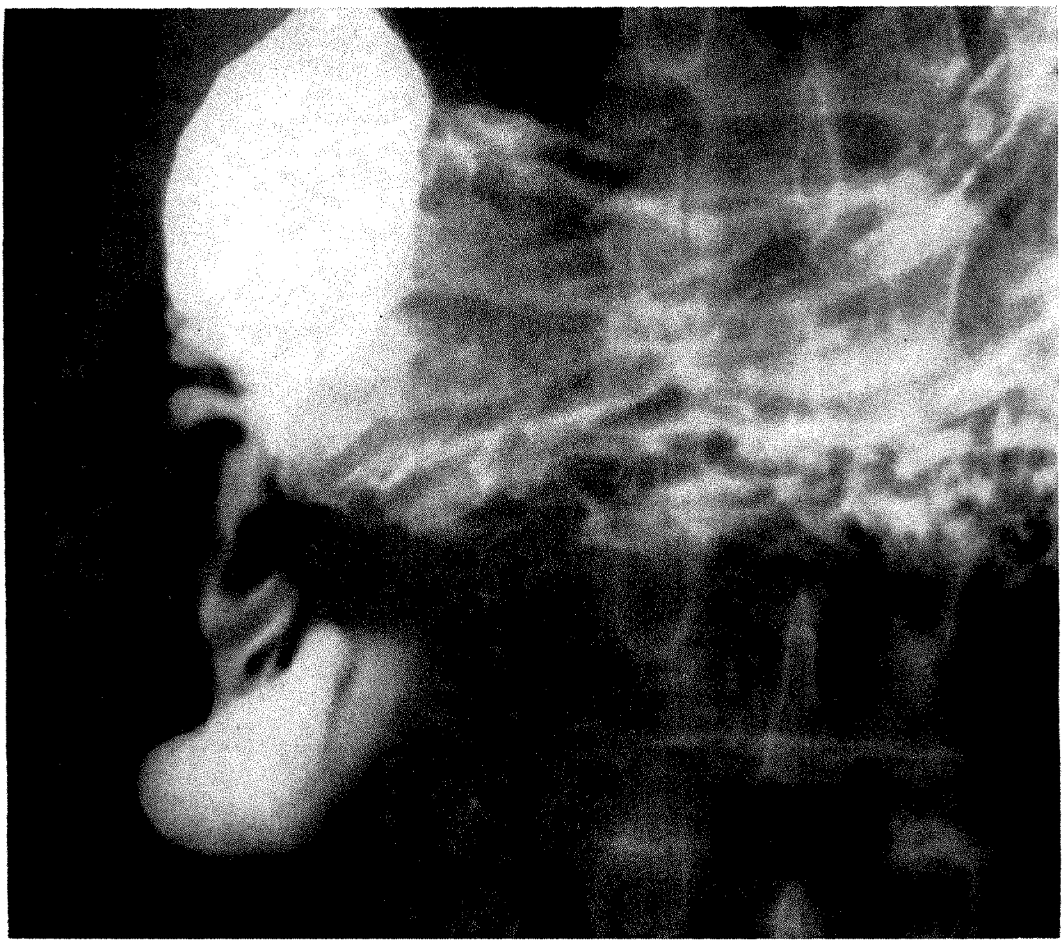

Fig. 3—Severe duodenal involvement with Crohn's disease producing stenosis, partial obstruction and "pseudodiverticula".

ever, the presenting symptomatology was upper abdominal pain without diarrhea, in two there was clinical evidence of gastric outlet obstruction and two pediatric patients were referred for upper abdominal pain and evaluation of growth retardation. Thus, while we experienced no examples of isolated duodenal Crohn's disease the clinical symptomatology was suggestive of peptic disease not Crohn's disease in a majority of instances. An awareness of the spectrum of radiographic abnormalities produced by duodenal Crohn's disease led to further radiographic evaluation of the colon and small bowel which demonstrated the characteristic radiologic appearance of Crohn's disease of the large or small bowel.

The severity of granulomatous change in the duodenum did not correlate with the degree of colonic or ileal involvement. Marked colonic and ileal enteritis was often present with only minimal duodenal abnormalities. Some patients, however, had severe duodenal involvement with fistula formation, abscess, or obstruction with only minor involvement of the remaining bowel.

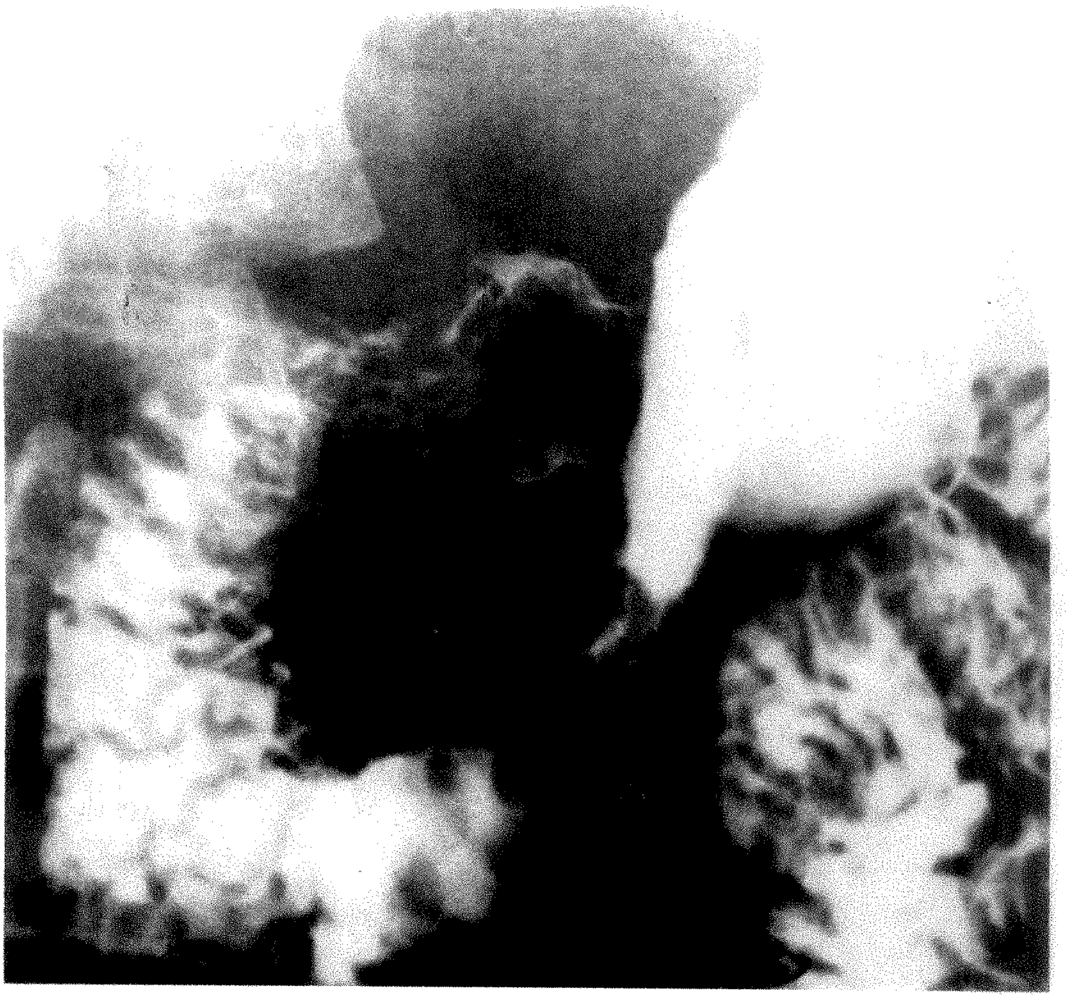

Fig. 4—Crohn's disease sparing the duodenal sweep but involving the third and fourth portion of the duodenum. These radiographic features must be distinguished from a malignancy of the duodenum.

The radiologic differential diagnosis of regional enteritis of the duodenum includes; duodenal scarring secondary to peptic ulcer disease, lymphoma, eosinophilic gastroenteritis, carcinoma of the duodenum or secondary invasion of the duodenum by an adjacent pancreatic neoplasm, duodenal spasm secondary to pancreatitis and giardiasis. A diagnosis of regional enteritis made solely on the basis of radiographic abnormalities within the duodenum is extremely difficult. An awareness, however, of the varied radiographic abnormalities produced by duodenal Crohn's disease may lead to a thorough examination of the small bowel and colon and allow a diagnosis of unsuspected Crohn's disease to be made.

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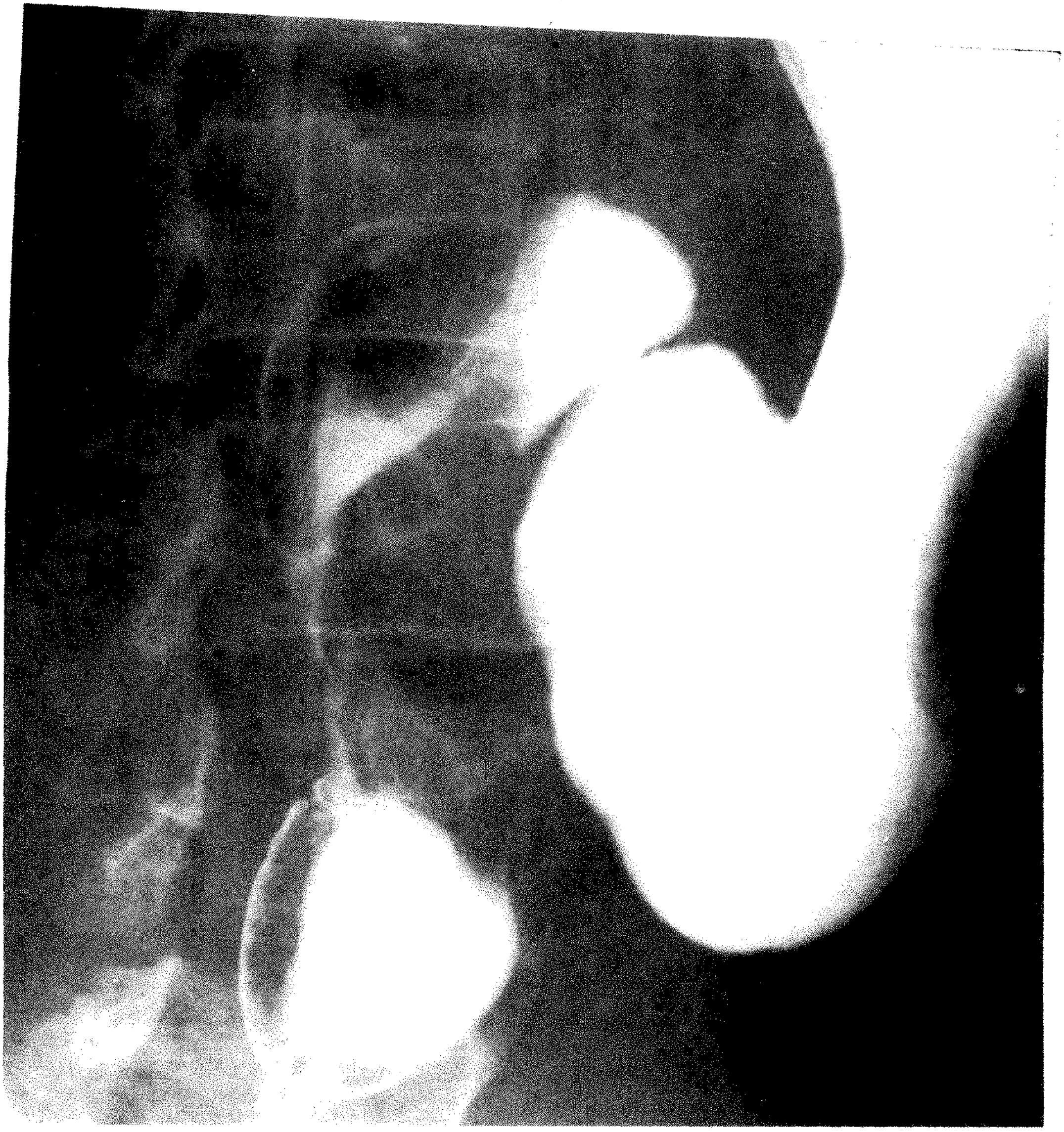

Fig. 5—Crohn's disease of the second portion of the duodenum resulting in gastric outlet obstruction.

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# The Last Page

## QUESTIONS IN GASTROENTEROLOGY

CHARLES G. HAZZI, M.D., F.A.C.G.*
New York, N. Y.

*The Last Page* appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. ESOPHAGITIS FOLLOWING IRRADIATION OF THE MEDIASTINUM:

   A. Results in frank ulceration most commonly and only abnormal motility least commonly, on x-rays.

   B. When it leads to stricture is best treated by surgery.

   C. May be treated effectively with local hydrocortisone injection via the esophagoscope when tight strictures prove refractory to dilatation.

   D. May be enhanced by adriamycin therapy.

   (Page 17)

2. REGARDING ACHALASIA AND GASTRIC CARCINOMA:

   A. Carcinoma of the gastric fundus may mimic achalasia using all criteria, clinical, radiologic, endoscopic and mamometric.

   B. When it invades the esophagus, gastric carcinoma usually results in subnormal sphincter pressure and diffuse esophageal spasm.

   C. In tumor-associated achalasia, the esophageal myenteric plexus is always involved.

   D. There is an increased incidence of carcinoma of the middle one-third of the esophagus in long-standing achalasia.

   (Page 24)

3. GASTROINTESTINAL BLEEDING IN AORTIC STENOSIS:

   A. Usually occurs in the age group below 50.

   B. Is due to vascular malformation (angiodysplasia) that can often be identified on barium studies.

   C. When studied angiographically reveals either an early-draining vein or a series of dilated tortuous vessels.

   D. May not recur if the aortic stenosis is surgically corrected.

   (Page 30)

4. CHIBA NEEDLE PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY:

   A. Demonstrates nondilated ducts in over two-thirds of such cases.

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* Assistant Professor of Clinical Medicine, New York University School of Medicine.

B. Will always demonstrate dilated ducts.

C. Will rule out bile duct lesions if no dilatation is found.

D. Should be followed by immediate laparotomy.

(Page 39)

5. PANCREATIC FUNCTION TEST USING A SYNTHETIC PEPTIDE:

A. Is based on the specific cleavage of Bz-ty-PABA by chymotrypsin, with recovery of PABA and derivatives in a six-hour urine collection.

B. Is as sensitive as secretin-pancreozymin tests in detecting minimal lesions of the pancreas.

C. With carcinoma, requires complete duct obstruction to be positive (low excretion).

D. Is abnormal after partial pancreatectomy only after removal of one-third to one-half of the pancreas.

(Page 45)

6. GASTRIN AND THE EXOCRINE PANCREAS:

A. In the experimental animal gastrin stimulates a marked increase in pancreatic enzyme output not dependent on passage of acid into the duodenum.

B. This effect has not been confirmed in man.

C. Elevated basal pancreatic flow and bicarbonate output in the ZE syndrome may be due to acid-induced release of secretin and CCK.

D. Gastrin has not been shown to produce hypertrophy of pancreatic acinar cells.

(Page 53)

7. REGARDING SURGERY FOR LOCALIZED DIVERTICULITIS:

A. The disease will often recur if immediate or subsequent elective resection are not performed.

B. Longitudinal myotomy is as effective as multiple transverse myotomies of *taeniae coli* for reversing colonic shortening, plication and narrowing.

C. Transverse taeniamyotomy may safely be used in the presence of acute inflammation.

D. It may be the operation of choice in the absence of extensive peridiverticulitis, abscess or perforation.

(Page 61)

8. GARDNER'S SYNDROME:

A. Has an incidence of 1/8,300 to 1/16,000 births and a dominant inheritance.

B. Should be suspected when the association of subcutaneous tumors and osteoma is found.

C. Presents with polyposis long before the soft tissue and bone lesions appear.

D. Requires total colectomy and ileostomy since the risk of malignant transformation of the adenomatous polyps is 100%.

(Page 68)

9. PANCREATIC CARCINOMA:

A. Usually produces a large, ulcerated intraluminal tumor when it invades the duodenum.

B. Is the fourth most common cause of death from cancer in men in the United States of America.

C. Arises as commonly in the uncinate process as in other parts of the pancreas.

D. May produce the same symptoms as duodenal carcinoma when it arises from the head of the pancreas.

(Page 74)

10. PANCREATIC PSEUDOCYSTS:

A. Usually follow recurrent alcoholic pancreatitis.

B. Have been detected with 100% accuracy using ultrasound.

C. Mediastinal extension of a pseudocyst never causes dysphagia.

D. The chest radiograph is usually normal in mediastinal pseudocyst.

(Page 78)

11. JEJUNAL MUCOSA AND MALNUTRITION:

    A. Villous atrophy usually follows gastric resection and pancreatic insufficiency.

    B. Chronic alcohol ingestion results in marked mucosal abnormalities on electron microscopy but not on light microscopy.

    C. Protein depletion results in marked ultrastructural changes.

    D. Luminal nutrients are necessary for the structural and functional integrity of the small bowel.

(Page 83)

12. GRANULOMATOUS GASTRITIS:

    A. Is always part of a systemic granulomatous disease, e.g. tuberculosis, sarcoidosis, regional enteritis.

    B. May result from foreign body ingestion.

    C. Usually results in pain, vomiting and weight loss and antral or pyloric narrowing on x-rays.

    D. May be indistinguishable from carcinoma without laparotomy.

(Page 90)

13. CHOLESTATIC JAUNDICE IN THE INFANT:

    A. Is most commonly due to either the neonatal hepatitis syndrome or extrahepatic biliary obstruction (atresia).

    B. Is never caused by infection or alpha$_1$ antitrypsin deficiency.

    C. When associated with high levels of lipoprotein-x in the serum that decrease after cholestyramine, is usually not due to biliary obstruction that requires surgery.

    D. Is probably due to biliary obstruction when there is low or absent excretion of $I^{131}$ rose bengal.

(Page 95)

14. REGARDING INTESTINAL MOTILITY:

    A. Slow waves are the main electrophysiologic property of small and large bowel smooth muscle and their frequency decreases from 12/min. in duodenum, to 7/min. in ileum and 3-6/min. in colon.

    B. CCK, gastrin and serotonin stimulate while secretin and glucagon inhibit, small bowel motility.

    C. Ileus results from overactivity of the inhibitory neural system.

    D. There is increased colonic motor activity in constipation and diminished activity in diarrhea.

(Page 101)

15. CROHN'S DISEASE OF THE DUODENUM:

    A. Is associated with previous small or large bowel involvement in most cases.

    B. Most commonly involves the descending duodenum.

    C. Is easily distinguished from carcinoma or peptic ulcer on x-rays.

    D. Leads to fistula formation as commonly as in ileal or colonic Crohn's disease.

(Page 107)

## ANSWERS TO QUESTIONS IN *The Last Page*

The following are the answers to the questions which appeared in *The Last Page* during the six months, commencing with the July, 1978 issue. The next set of answers for the period from January to June, 1979, will appear in the July, 1979 issue.

*July, 1978*

1. All
2. B
3. All
4. A,D
5. B,C
6. B,C,D
7. D
8. A,D
9. A,B,D
10. A,D
11. A,B,C
12. All
13. A,B,C
14. All

*August, 1978*

1. A,C
2. All
3. A,B,D
4. A,B,C
5. B,D
6. A,B
7. All
8. A,C,D
9. A,C,D
10. B,C
11. A,C,D
12. B,C
13. B,C,D
14. All
15. B,C,D

*September, 1978*

1. All
2. C
3. All
4. B,C,D
5. A,B,D
6. A,B
7. B
8. A,B,D
9. All
10. D
11. A,C,D
12. C,D
13. A,B,C
14. All

*October, 1978*

1. A,B,D
2. B,C,D
3. A,B
4. A
5. All
6. D
7. All
8. B,C
9. B,C,D
10. A,C,D
11. All
12. A,B,D
13. A,B,C
14. A,B,C

*November, 1978*

1. A,C,D
2. B,D
3. A.B,C
4. All
5. None
6. B.C,D
7. B,C
8. All
9. All
10. A,B
11. All
12. B,C
13. D
14. C
15. A,C,D
16. A,B,C,F
17. A,C

*December, 1978*

1. A,D
2. C,D
3. B,C,D
4. C,D
5. A,C
6. A,C
7. A,C
8. A,B
9. A,D
10. B,C
11. A,C,D
12. B,D
13. A,C
14. C,D
15. B,C
16. B

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# EDITORIAL

Editors and their staffs must change periodically and so this issue of the Journal carries a new masthead. The purpose of this editorial is to allow the new editors to introduce themselves, to describe some changes in the features and content of the Journal and to renew a welcome to our readers to submit papers and letters of interest to their colleagues in clinical gastroenterology.

Both the Editor-in-Chief and the Associate Editor are gastroenterologists at New York University School of Medicine. Our proximity to the Journal offices in New York will allow us to continue to receive manuscripts and letters at the Journal office, where the Managing Editor, Mr. Daniel Weiss and his staff can so efficiently direct the many details of review and correspondence.

The editors are most grateful to our predecessor as Editor-in-Chief, David A. Dreiling, M.D., F.A.C.G. for his advice and warm support during this transition period. Indeed, as with any journal, the mandatory time between receipt of a manuscript and publication has required that Dr. Dreiling guide the content of the Journal for perhaps six months into 1979. Fortunately we will not lose his editorial services, for he has agreed to accept assignments as Foreign Editor and Book Review Editor, both areas of his particular interest and expertise.

Emanuel Lebenthal, M.D., F.A.C.G., Chief of the Division of Gastroenterology and Nutrition at Buffalo Children's Hospital, will serve as editor for pediatric gastroenterology. We look forward to a much expanded section in the Journal for this important specialty. Richard H. Marshak, M.D., F.A.C.G. will continue to edit The Radiology Corner and Jerome D. Waye, M.D., F.A.C.G. will direct The Endoscopy Corner. The Last Page, our section of self-test questions based on the contents of each issue, will be prepared by Charles C. Hazzi, M.D., F.A.C.G.

A new series, State of the Art, is concerned with bringing up to date our knowledge of some of the major topics in gastroenterology. Designed to be of practical, day-to-day value to the practicing gastroenterologist, the reviews will be prepared by authorities in their respective fields. The series will continue under the editorship of Walter Harvey Jacobs, M.D., F.A.C.G.

The Editorial Advisory Board serves the essential function of reviewing manuscripts and also providing counsel in the operations of the Journal. The editors want to express their thanks to those members whose terms have been completed and to welcome the new members of the Board.

We begin our terms as editors with enthusiasm and with the conviction that the Journal will continue to grow and to serve the evolving needs of the clinical gastroenterologist.

Arthur E. Lindner, M.D., F.A.C.G.
Michael Ruoff, M.D., F.A.C.G.

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# NEWS NOTES

## NEW OFFICERS OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY

Election of Officers, Trustees and Governors took place at the Annual Meeting of the Fellowship of the American College of Gastroenterology on Monday, 25 September 1978 at The Marriott in Denver, Colo.

Elected officers were: President-elect, Sidney J. Winawer, M.D., F.A.C.G., New York, N. Y.; Vice Presidents, Ivan T. Beck, M.D., F.A.C.G., Kingston, Ont. Canada and Burton I. Korelitz, M.D., F.A.C.G., New York, N. Y.; Treasurer, David A. Dreiling, M.D., F.A.C.G., New York, N. Y. and re-elected Secretary-General, John T. Galambos, M.D., F.A.C.G., Atlanta, Ga.

Newly elected members of the Board of Trustees were: Philip S. Bentlif, M.D., F.A.C.G., Houston, Texas; Arthur E. Cocco, M.D., F.A.C.G., Baltimore, Md.; Malcolm C. Veidenheimer, M.D., F.A.C.G., Boston, Mass.; Richard L. Wechsler, M.D., F.A.C.G., Pittsburgh, Pa.; James L. Achord, M.D., F.A.C.G., Jackson, Miss.; Basil I. Hirschowitz, M.D., F.A.C.G., Birmingham, Ala.

Re-elected were: Robert J. Priest, M.D., F.A.C.G., Grosse Pointe, Mich. and James L. A. Roth, M.D., F.A.C.G., Philadelphia, Pa.

Re-elected to the Board of Governors were: Angelo E. Dagradi, M.D., F.A.C.G., Long Beach, Calif.; J. S. Shah, M.D., F.A.C.G., Bombay, India; Victor M. Rosenoer, M.D., F.A.C.G., Boston, Mass. and Joseph H. Hardison, Jr., M.D., F.A.C.G., Raleigh, N. C.

Newly elected for a three-year term were: E. Marvin Sokol, M.D., F.A.C.G., Huntington, N. Y.; Perry Hookman, M.D., F.A.C.G., Cheverly, Md. and Herbert L. Hyman, M.D., F.A.C.G., Allentown, Pa.

At the Annual Meeting of the Board of Governors held on Tuesday, 26 September 1978, Robert L. Berger, M.D., F.A.C.G. of Hollywood, Fla. was re-elected Chairman of the Board of Governors.

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## AUXILIARY OFFICERS ELECTED

At the Annual Meeting of the Auxiliary of the American College of Gastroenterology which was held in Denver, Colo., on Wednesday, 27 September 1978, Mrs. David A. Dreiling, New York, N. Y. was elected President; Mrs. Robert L. Berger, Hollywood, Fla., President-elect; Mrs. James B. Chandler, Jr., Temple, Texas, 1st Vice President; Mrs. Murrel H. Kaplan, New Orleans, La., 2nd Vice President; Mrs. L. E. Chapin, Fullerton, Calif., 3rd Vice President; Mrs. Harold H. Scudamore, Monroe, Wis., Secretary; Mrs. Francis M. Maple, Springfield, Mo., Treasurer and Auxiliary Philanthropic Fund Chairman.

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## 1978 RORER AWARDS CONTEST WINNERS

Awards for the best papers published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY, the official publication of the American College of Gastroenterology, during the 12 months ended 31 May 1978, were announced at the Annual Convocation of the College, in Denver, Colo., on Sunday, 24 September 1978.

These awards are given by the College in cooperation with William H. Rorer, Inc. of Fort Washington, Pa.

The recipients of the First Prize of $500.00 were Yutaka Matsuo, M.D. and Atsuko Seki, M.D. of Tokyo, Japan for their paper entitled "The Coordination of Gastrointestinal Hormones and the Autonomic Nerves". The work was done at The Third Department of Medicine of the Faculty of

Medicine of the University of Tokyo and was published in the January, 1978 issue.

Awarded Second Prize of $300.00 were Orlando Bordalo, M.D., F.A.C.G., Diaz Concalves, M.D., Manuela Noronha, M.D., F.A.C.G., M. Luisa Cristina, M.D., Amelia Salgadinhos, of Lisbon, Portugal and David A. Dreiling, M.D., F.A.C.G., of New York, N. Y. The paper "Newer Concept for the Pathogenesis of Chronic Alcoholic Pancreatitis" appeared in the September, 1977 issue.

The Third Prize of $200.00 went to J. Edward Berk, M.D., F.A.C.G. of Irvine, Calif., Junnosuke Shimamura, M.D., of Okayama-ken, Japan and Louis Fridhandler, Ph.D., of Orange, Calif. The paper which was published in the December, 1977 issue was entitled "Tumor-associated Hyperamylasemia" and was based upon work done at the Division of Gastroenterology, College of Medicine, University of California, Irvine.

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### ANNUAL RICHARD H. MARSHAK AWARD

Roger K. Harned, M.D. and Gerald L. Wolf, M.D., Ph.D. of Omaha, Neb., received the Annual Richard H. Marshak Award for the best Radiology paper published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY during the 12-month period which ended 31 May 1978. The award was for the paper entitled "Is an Air-Fluid Level Within a Gastric Ulcer a Reliable Roentgen Sign of Benignancy?", which appeared in the June, 1977 issue of the Journal.

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# BOOK REVIEWS FOR GASTROENTEROLOGISTS

**Gastroenterology-An Integrated Course; 2nd edition: by Iain E. Gillespie, M.D. and T. J. Thomson, M.D. 292 pages, illustrated. Churchill Livingstone, New York, NY., 1977. Price $9.95.**

Gastroenterology, an integrated course, has now been published in its second edition. It is a multi-authored text edited by I. E. Gillespie and T. J. Thomson and has been especially prepared to be used as an accompaniment for students during their instruction in clinical medicine, in particular during a gastroenterology rotation.

The book is divided according to organ systems and contains brief descriptions of these systems, including anatomical, physiological and therapeutic considerations. For a book this size, this large task leads to very superficial coverage. Most of the authors are surgeons and, therefore, an undue emphasis has been placed upon treatment, particularly the surgical approach to gastrointestinal disease. It would be more meaningful for a student to have a book which gives an approach to classification and diagnosis of disease, rather than a brief descriptive passage of a disease entity and therapeutic comment, both of which can be better obtained in one of the other standard text books.

STANLEY N. BRAND, M.D.

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**The Origins of the Healing Art: by Irving I. Edgar, M.D. 246 pages, illustrated. Philosophical Library, Inc., New York, NY, 1978. Price $9.50.**

The origins of the healing art is written by Irving I. Edgar, A.M., M.D., F.A.C.P., who was special lecturer in medical history at Wayne State University during the period when Professor William J. Stapleton was head of the Department. The book is an interesting historical review of the major events which marked the gradual evolution of medicine from its simplest and most primitive origins to the important place it plays in modern society. Although it is separated into several major sections which deal with infections, the development of preventative medicine, the circulation of the blood, psychiatry, pharmacology, pathology and surgery, it attempts to integrate these subjects into a comprehensive whole.

Modern medicine was molded by contributions of a number of great men, the fathers of the art and science of medicine: Harvey, Maimomnides, Virchow, Semmelweiss, Lord Lister and Freud. Recognition is given to each in an appropriate section. Interesting historical anecdotes are used to emphasize the gradual evolution of medicine today. The petty jealousies which resulted in the tragic martyrdom of Semmelweiss and set back medicine a half a century is a particularly sad episode in a history which is filled with greatness, sacrifice and dedication of man to man. This book should be on the book shelf of all physicians, nurses and historians. It is a well written and absorbing account of our history.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G.

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**Current Concepts in Pediatric Radiology: edited by O. Eklof, M.D. 150 pages, illustrated. Springer-Verlag New York Inc., Secaucus, NJ, 1977. Price $24.90.**

This small volume edited by Dr. Eklof of Stockholm, Sweden is based on a series of lectures given at the First International Postgraduate course sponsored by the Swedish Society of Pediatric Radiology. It consists of a series of excellent articles by experts in the field of Pediatric Radiology. These authors come from South Africa: Drs. Cremin, Boston and Brockwell; England: Ashley and Chrispin; Brussels: Cadranel and Cremer; Switzerland: Giedion; Sweden: Thander; USA: Girdany, Silverman and Poznanski and others from the USA, France and Germany. It covers a wide variety of pediatric radiologic topics from the respiratory, gastrointestinal and genitourinary tracts to the brain and spinal cord. The articles in general are well written, with superb illustrations and figures in a clear glossy print. This is an excellent review of pediatric radiology for the pediatrician, pediatric surgeon, radiologist and general surgeons with an interest in childhood diseases.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G.

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**How To Get Along With Your Stomach: by Nancy Nugent, 271 pages, illustrated. Little, Brown and Company, Boston, MA, 1978. Price $8.95.**

*How To Get Along With Your Stomach* written by Nancy Nugent, is a comprehensive book which considers systematically both psychological and organic disease of the gastrointestinal tract from the esophagus to the colon. Written by a lay person, it includes an introductory section on the digestive system as a whole and a chapter on Basic Anatomy. The factual information on the many digestive diseases discussed is, in general, accurate and often represents the latest information obtained from the medical literature. The book is well written and easy to read and comprehend. Of particular value is the section on the Heimlich maneuver, a technic which should be widely publicized and has already saved over 800 lives. This book can be highly recommended to all who are interested in a comprehensive review of digestive diseases.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G.

### Postcholecystectomy Syndromes: A Clinical Approach to Etiology, Diagnosis, and Management: by Clarence J. Schein, M.D. 264 pages, Illustrated. Harper & Row, Publishers, Inc., Hagerstown, MD, 1978. Price $25.00.

Clarence J. Schein has presented us with his customary masterly review of problems concerning the biliary tract. There really is nothing comparable to it in the modern literature.

I can find only one point of major disagreement. Dr. Schein, a classmate of mine at medical school, does quote my paper indicating an experience which suggests neuropsychiatric factors as the major pathogenetic mechanism. He does not disagree with this thesis but spends little time or space upon it. This might leave an impression that there is usually an organic basis to this so-called syndrome, an impression often resulting in unnecessary surgery. A small carp dwarfed by the general excellence of the text.

David A. Dreiling, M.D., F.A.C.G.

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### Topics in Gastroenterology: 5th edition: edited by S. C. Truelove, M.D. and Emanuel Lee. J. B. Lippincott Company, Philadelphia, PA, 1978 Price $39.50.

This is the fifth in the series of written versions of the Annual Oxford Course in Postgraduate Gastroenterology. The faculty and articles are top notch. The topics covered in this edition are Cancer of the Large Bowel, Drugs and the Liver, Surgical Aspects of Bile Duct Disease and some miscellaneous considerations included in which are Vagotomy, The Carcinoid Syndrome, The Virology and Pathogenesis of Acute Infectious Diarrhea, Yersinia Infections, and Coeliac Disease.

David A. Dreiling, M.D., F.A.C.G.

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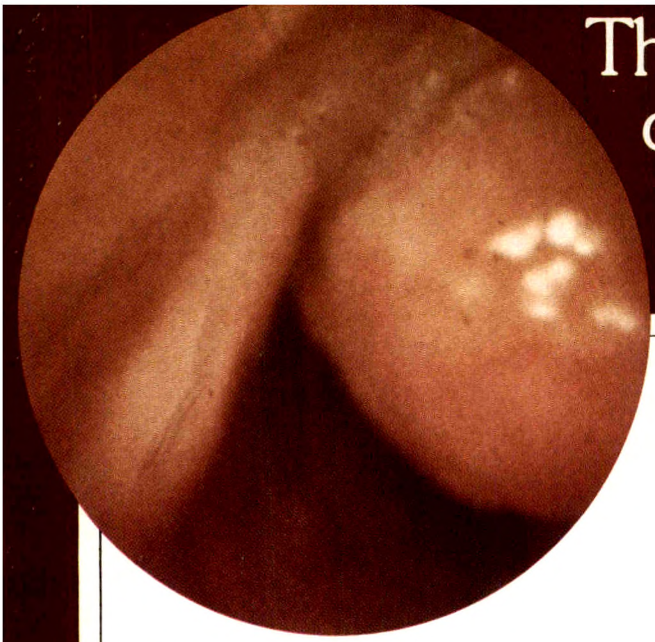
### Radiologic Diagnosis of Polyps and Carcinoma of the Large Bowel: by Masakzu Maruyama, M.D. 262 pages, illustrated. Igaku-Shoin Medical Publishers, Inc., New York, NY, 1978. Price $52.00.

While x-ray, endoscopy and biopsy are recognized as the essential tools in the diagnosis of colonic polyps and neoplasms, endoscopy has recently monopolized the footlights. Dr. Maruyama, using an unusual technic of case presentation analysis, has demonstrated the scope and limitation of the radiologic approach. In over 400 illustrations the author shows his mastery of the double contrast technic with air. The x-ray reproductions are excellent and there is fine correlation with gross and microscopic findings. Very well done.

David A. Dreiling, M.D., F.A.C.G.



# The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.

# What is the diagnosis?

## Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

*Esophagoscopy* was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas,* which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

# Endoscopy

## -confirmatory or contradictory-

# a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

**Postcholecystectomy Syndromes: A Clinical Approach to Etiology, Diagnosis, and Management: by Clarence J. Schein, M.D. 264 pages, Illustrated. Harper & Row, Publishers, Inc., Hagerstown, MD, 1978. Price $25.00.**

Clarence J. Schein has presented us with his customary masterly review of problems concerning the biliary tract. There really is nothing comparable to it in the modern literature.

I can find only one point of major disagreement. Dr. Schein, a classmate of mine at medical school, does quote my paper indicating an experience which suggests neuropsychiatric factors as the major pathogenetic mechanism. He does not disagree with this thesis but spends little time or space upon it. This might leave an impression that there is usually an organic basis to this so-called syndrome, an impression often resulting in unnecessary surgery. A small carp dwarfed by the general excellence of the text.

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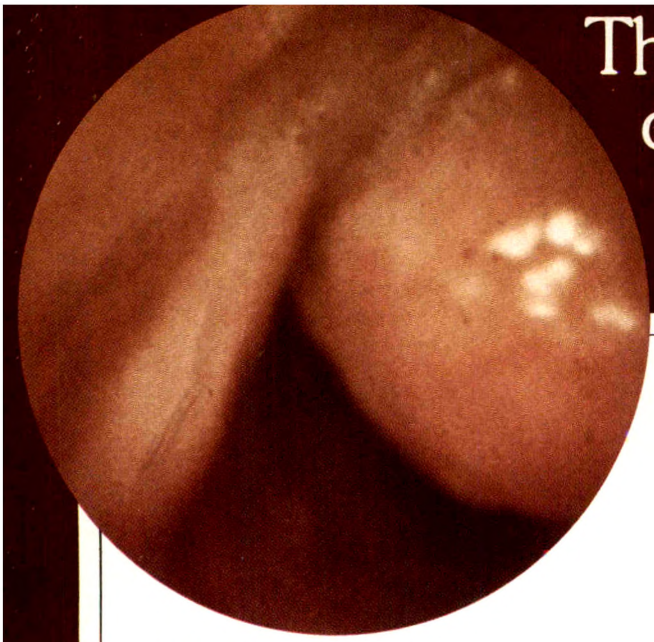

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## MEETINGS OF INTEREST

**44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.**

**Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.**

A Symposium on Gastroenterology, University of California School of Medicine, San Francisco and the Central California Committee for Gastroenterology, Ahwahnee, Yosemite National Park, CA, 11-14 March 1979.

Eighth Annual William Beaumont Gastrointestinal Symposium, William Beaumont Army Medical Center, El Paso, TX, 21-23 March 1979.

**Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.**

A Day in the G.I. Tract—An Update for the Generalist and Specialist, Divisions of Gastrointestinal and Liver Diseases, Albert Einstein College of Medicine and Montefiore Hospital and Medical Center, Riklis Auditorium, Albert Einstein College of Medicine, Bronx, NY, 29 April 1979.

Current Concepts in Gastrointestinal Disease, Postgraduate Course of the American Gastroenterological Association, Rivergate Convention Center, New Orleans, LA, 19, 20 May 1979.

Eightieth Annual Meeting of the American Gastroenterological Association, New Orleans Hilton, New Orleans, LA, 21-23 May 1979.

Endoscopy 1979, Postgraduate Course of the American Society for Gastrointestinal Endoscopy, New Orleans, LA, 24, 25 May 1979.

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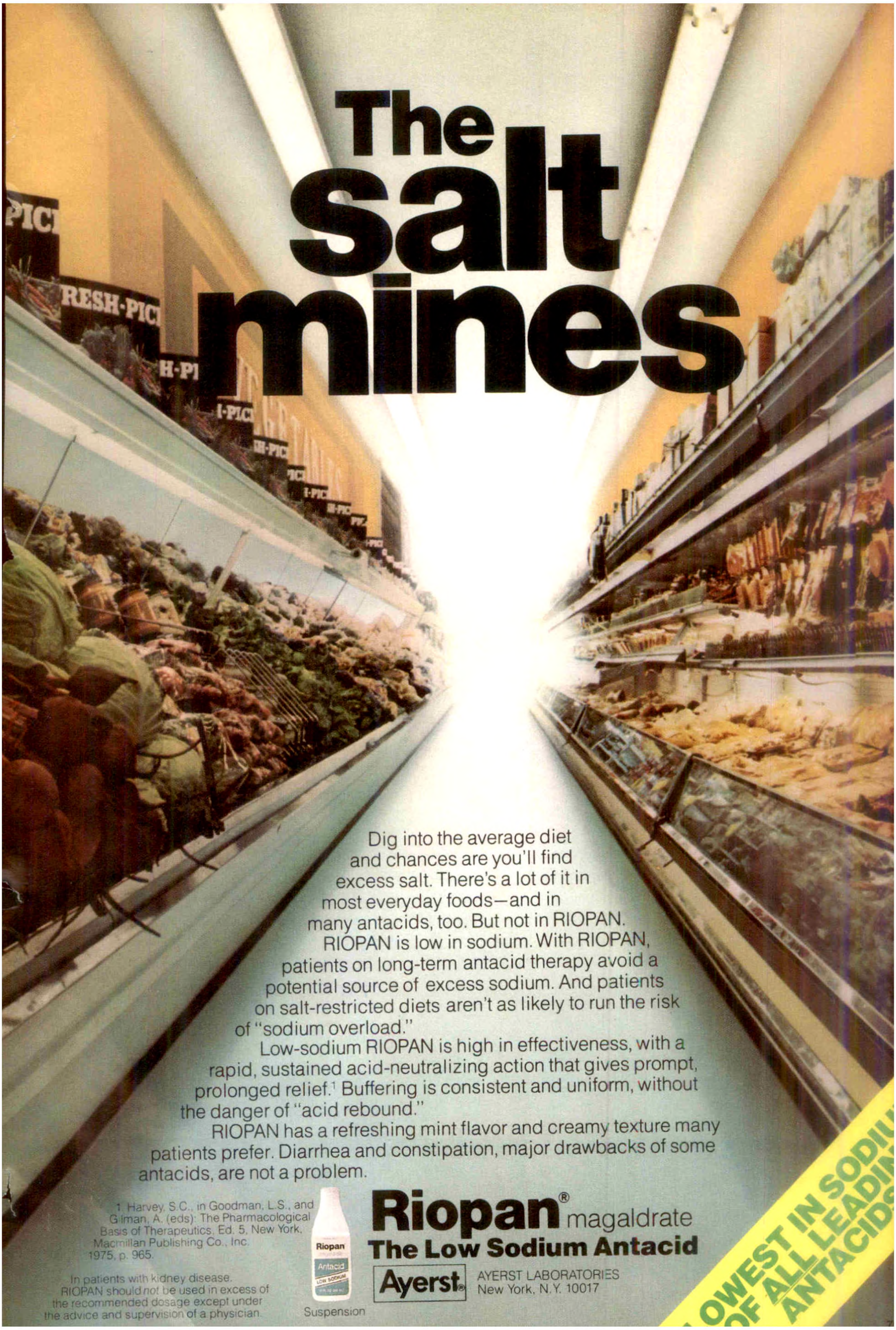

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[1] Harvey, S.C., in Goodman, L.S., and Gilman, A. (eds): The Pharmacological Basis of Therapeutics, Ed. 5, New York, Macmillan Publishing Co., Inc. 1975, p. 965.

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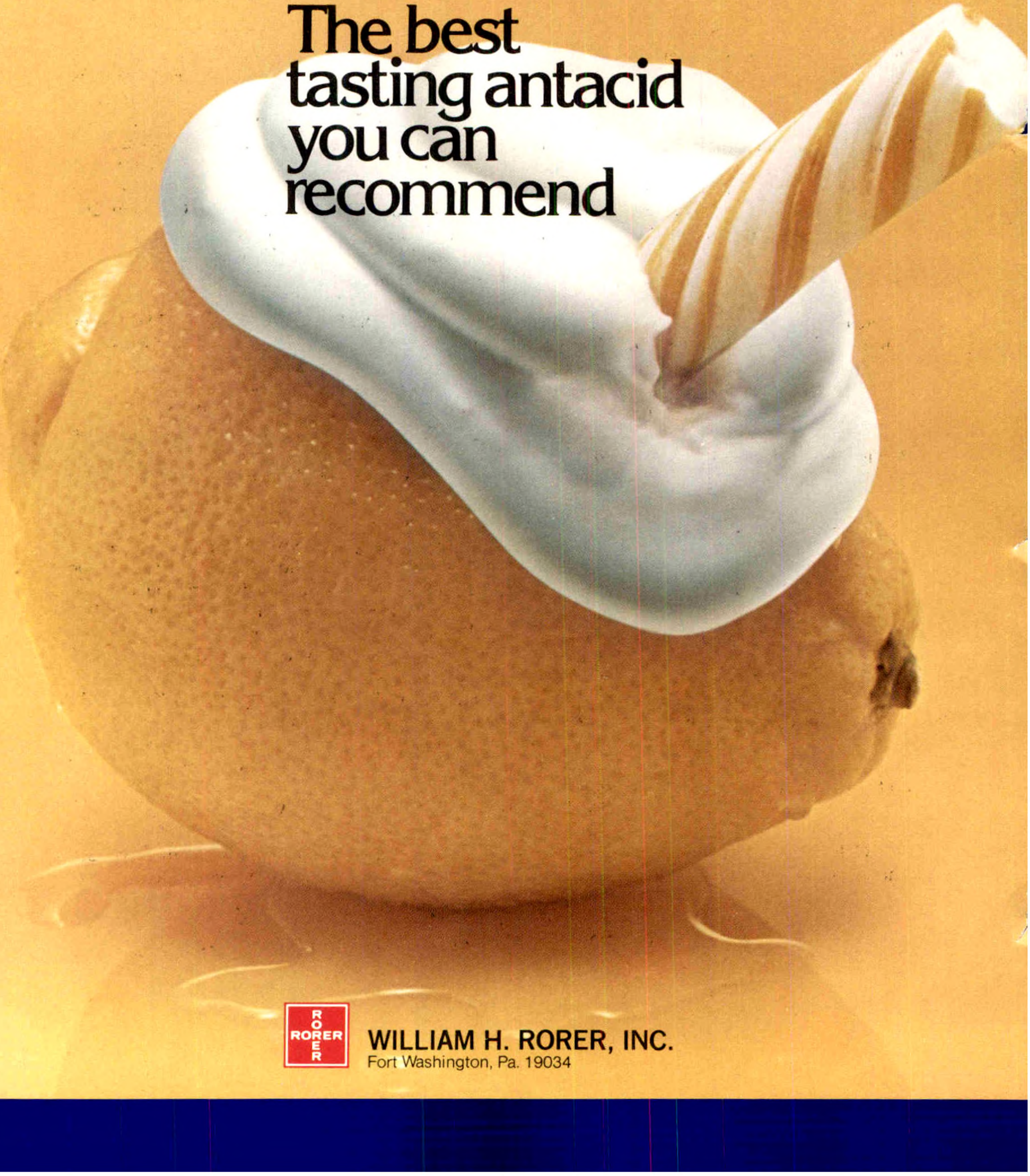

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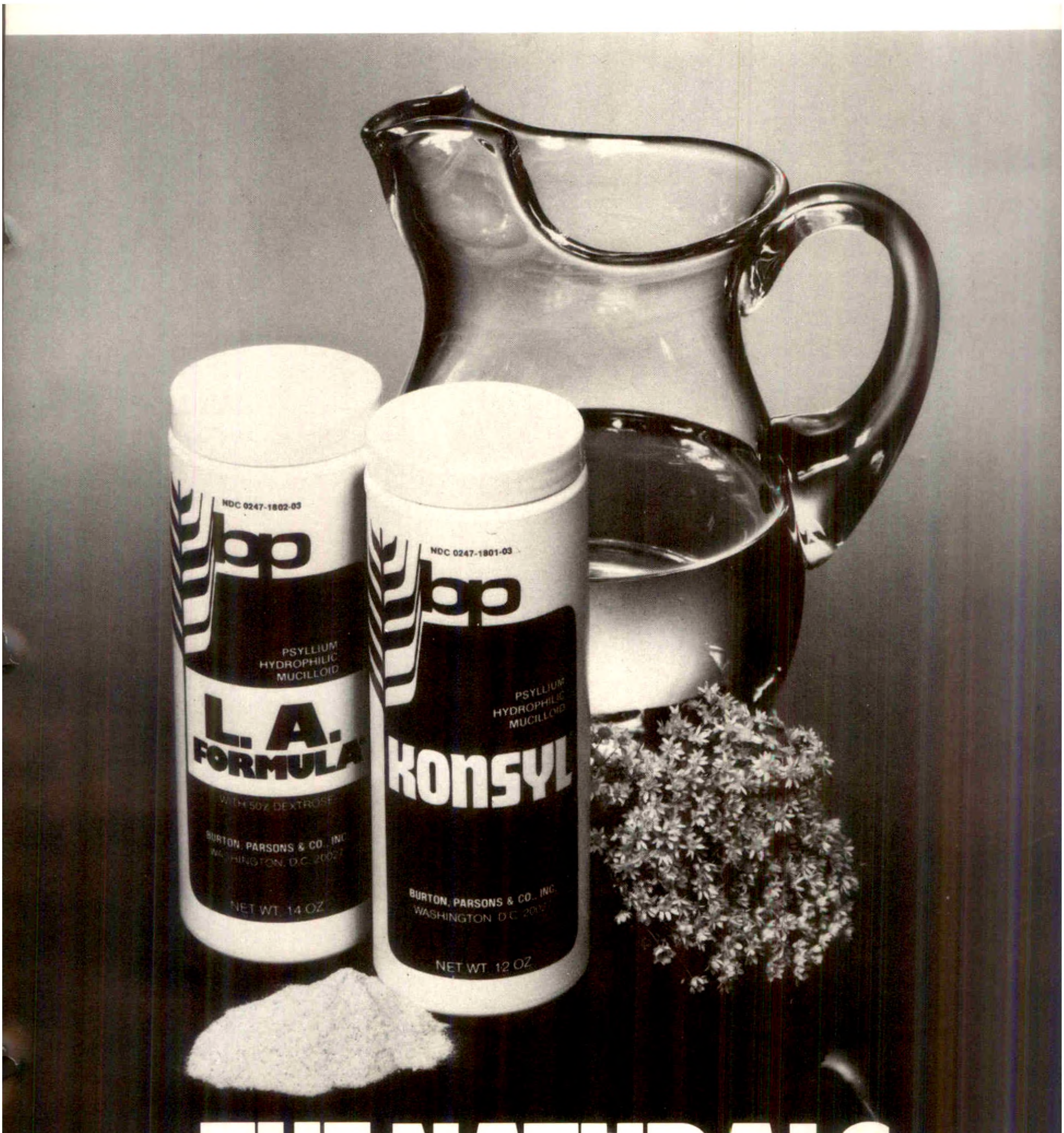
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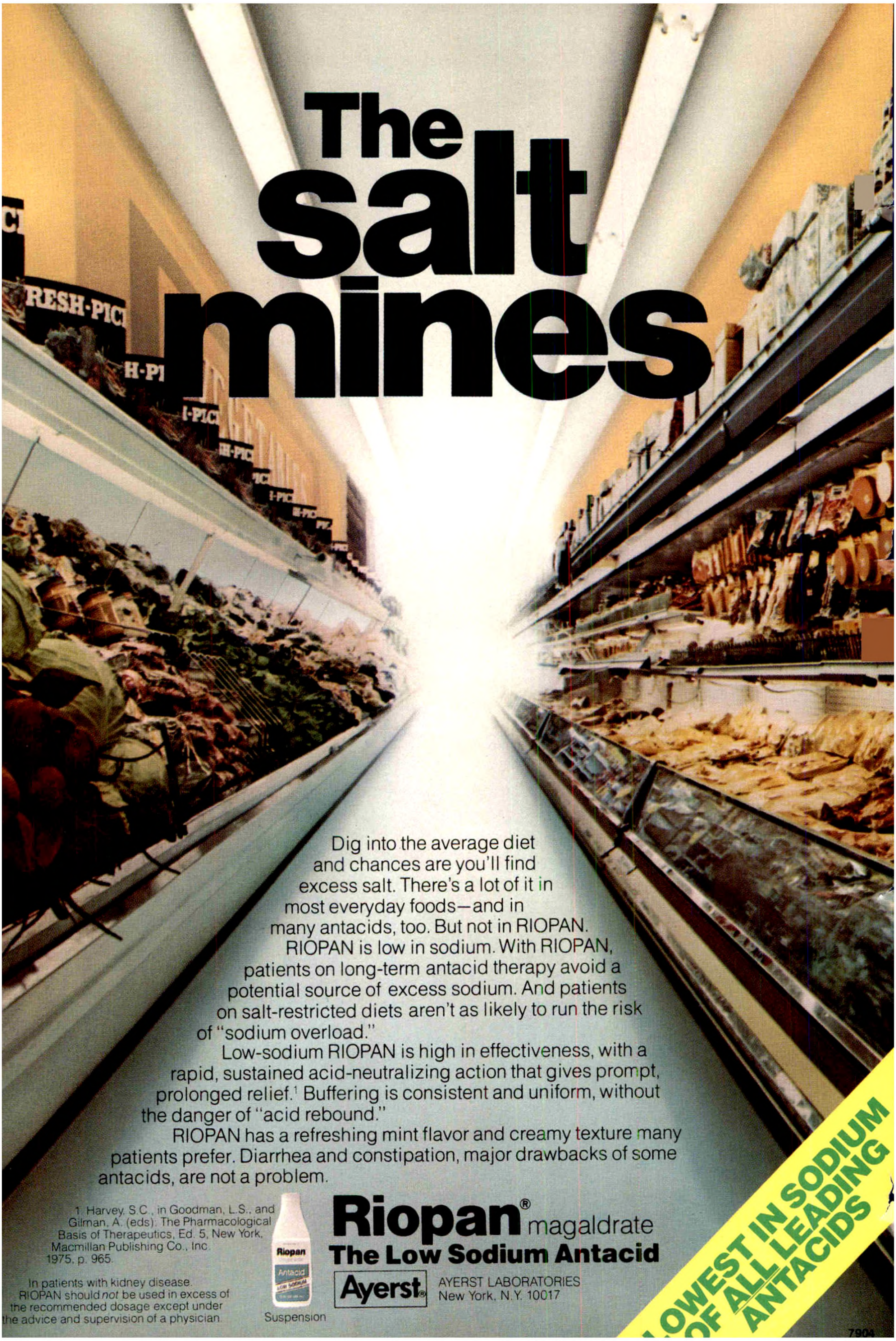

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Vol. 71, No. 2 FEBRUARY, 1979

THE American Journal OF Gastroenterology

(Formerly The Review of Gastroenterology)

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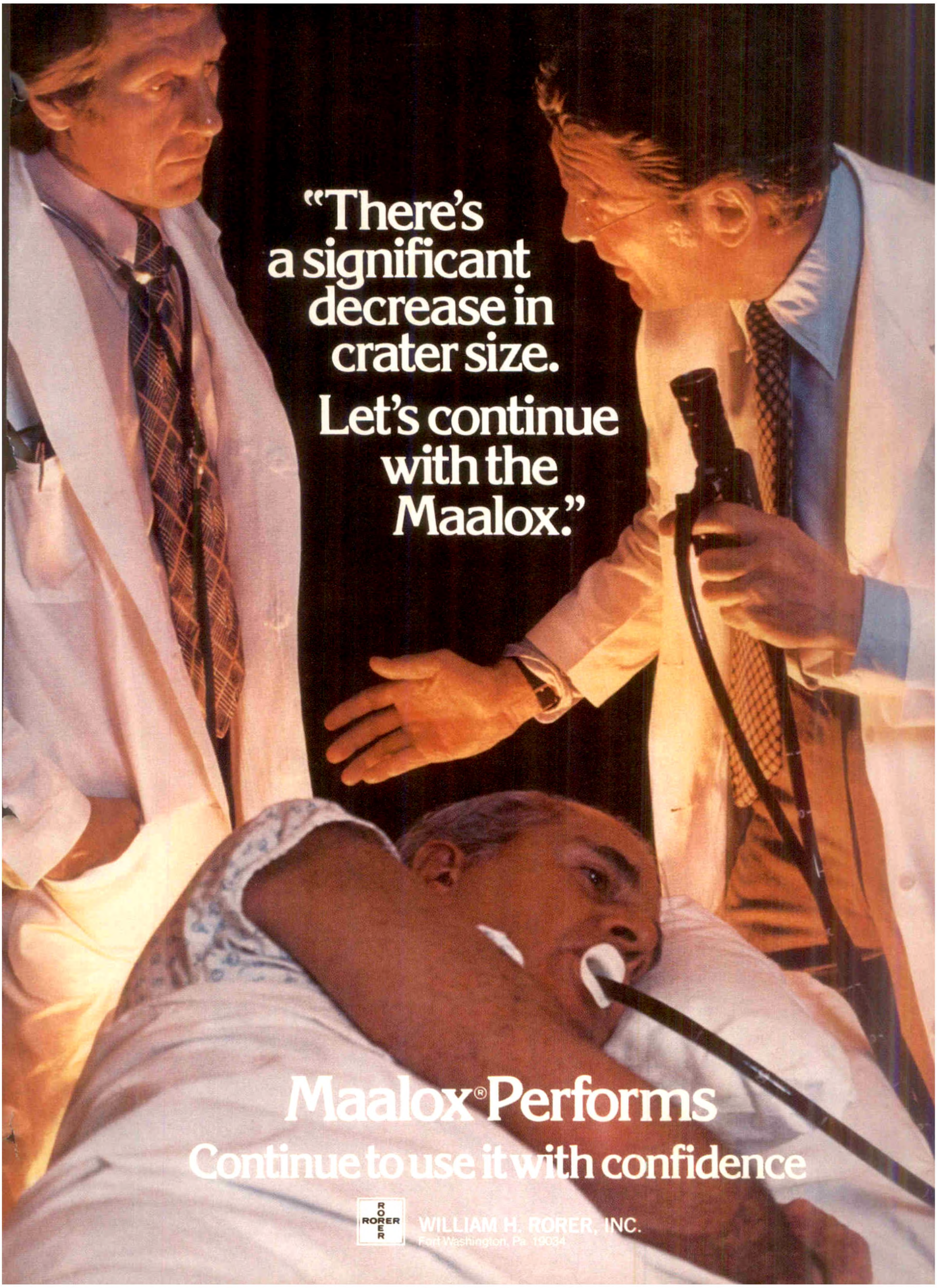
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3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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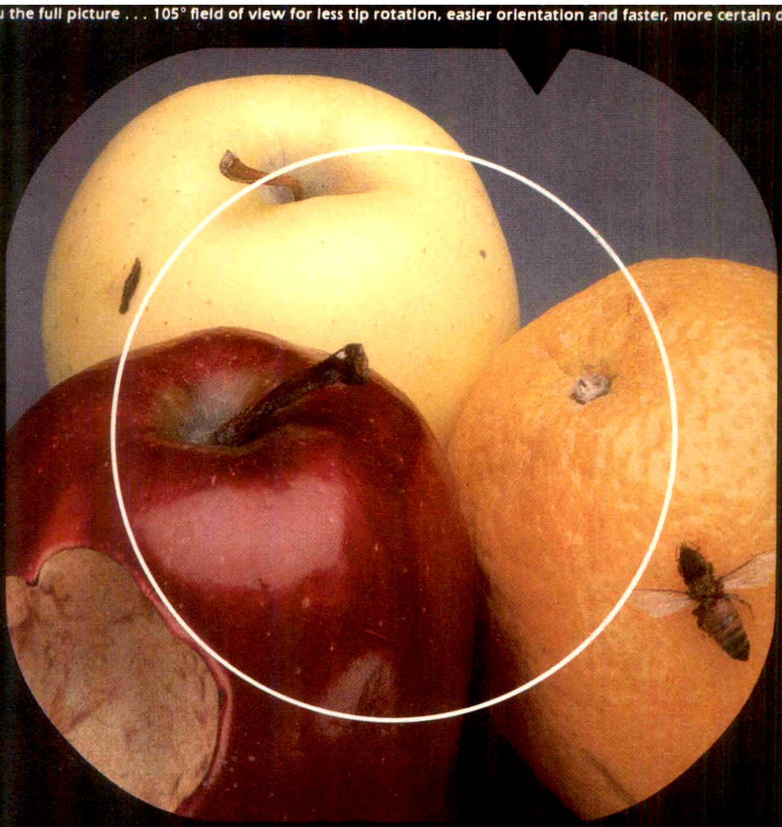

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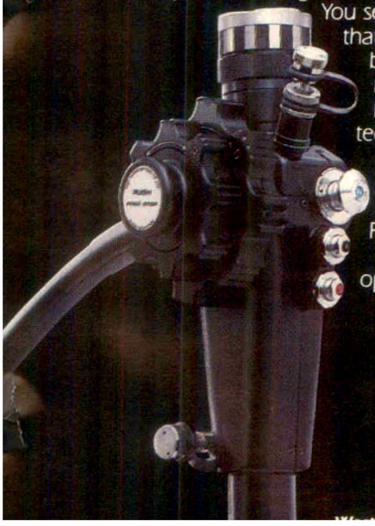

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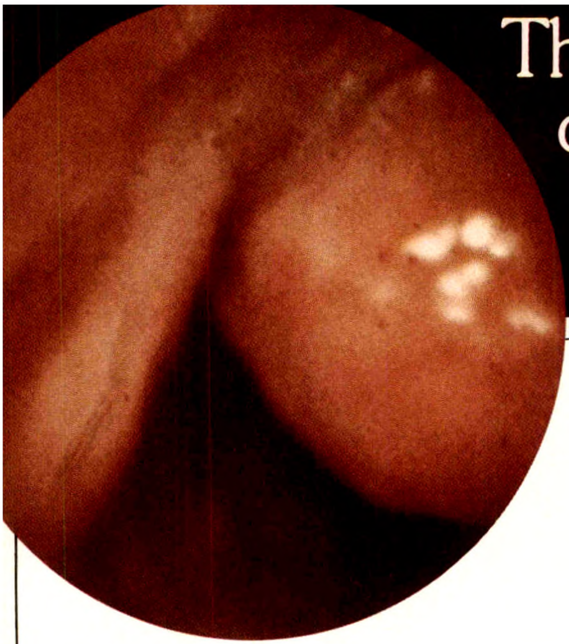

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Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

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As with all anticholinergics, inhibition of lactation may occur.

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## MEETINGS OF INTEREST

**44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.**

**Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.**

**Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.**

A Day in the G.I. Tract—An Update for the Generalist and Specialist, Divisions of Gastrointestinal and Liver Diseases, Albert Einstein College of Medicine and Montefiore Hospital and Medical Center, Riklis Auditorium, Albert Einstein College of Medicine, Bronx, NY, 29 April 1979.

Current Concepts in Gastrointestinal Disease, Postgraduate Course of the American Gastroenterological Association, Rivergate Convention Center, New Orleans, LA, 19, 20 May 1979.

Eightieth Annual Meeting of the American Gastroenterological Association, New Orleans Hilton, New Orleans, LA, 21-23 May 1979.

Endoscopy 1979, Postgraduate Course of the American Society for Gastrointestinal Endoscopy, New Orleans, LA, 24, 25 May 1979.

International Symposium on Infant Nutrition and the Development of the Gastrointestinal Tract, State University of New York at Buffalo, Department of Pediatrics and Children's Hospital, Buffalo, Niagara Hilton, Niagara Falls, NY, 3-8 June 1979.

Frontiers of Science and the Liver—A Symposium, In Honor of the 75th Birthday of Hans Popper, M.D., F.A.C.G. (Hon.), Mount Sinai School of Medicine of the City University of New York, 1 Gustave Levy Place, New York, N. Y., 5 June 1979.

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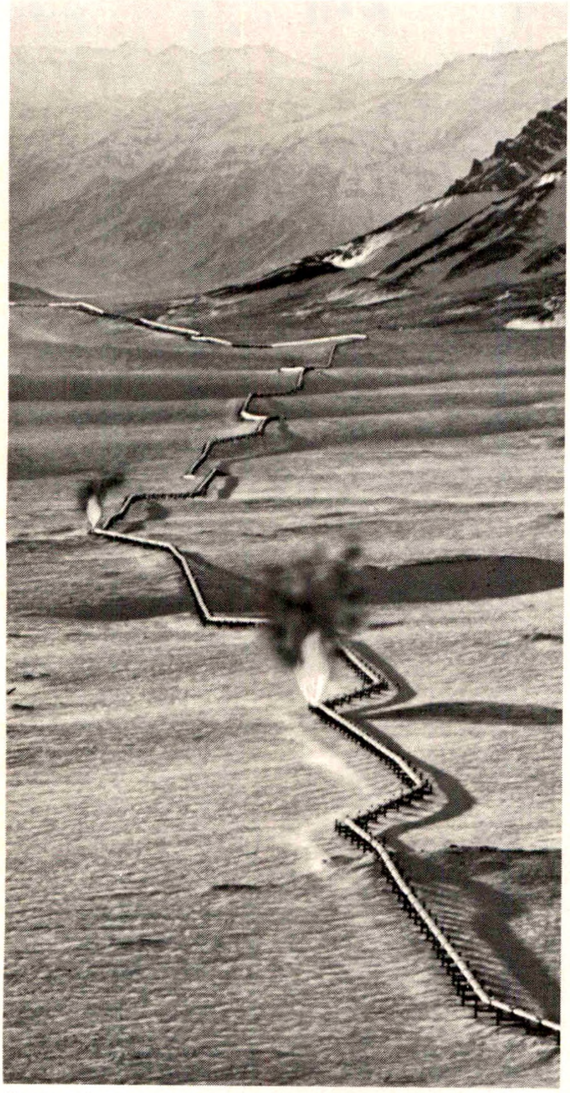

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**WARNINGS:** The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

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**Gastrointestinal reactions:** Anorexia, nausea, emesis, abdominal pains, diarrhea, bloody diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

**CNS reactions:** Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.

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**References:**

1. Dissanayake, A.S. and Truelove, S.C.: Gut 14:923-926, Dec. 1973.
2. Bargen, J.A.: Amer. Surg. 28:630-637, Sept. 1962.
3. Hightower, N.C., Jr., et al.: Amer. J. Digest. Dis. 3:722-733, 861-876, 931-941, Oct., Nov., Dec. 1958.
4. Roth, J.L.A.: Chapter 69, in Bockus, H. (ed.): Gastroenterology, Vol. II, W.B. Saunders Company.
5. Riis, P., et al.: Scand. J. Gastroenterol. 8:71-74, 1973.
6. Goldstein, F. and Thornton, J.J.: Consultant 14:96-103, July 1974.

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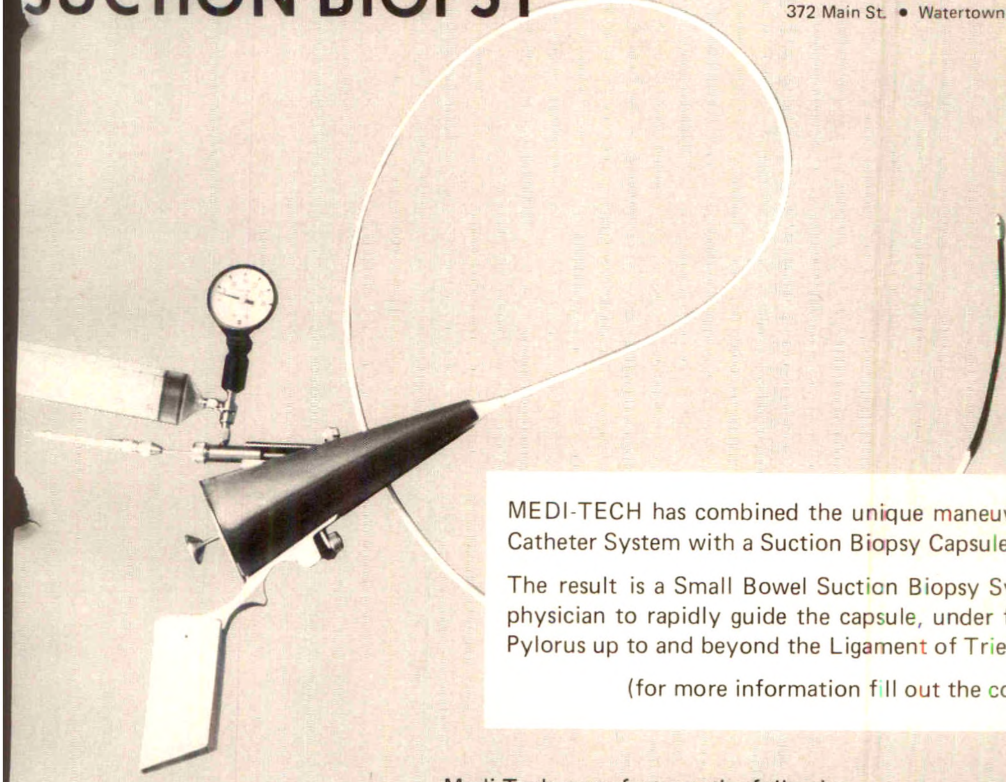

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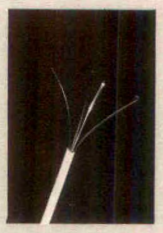

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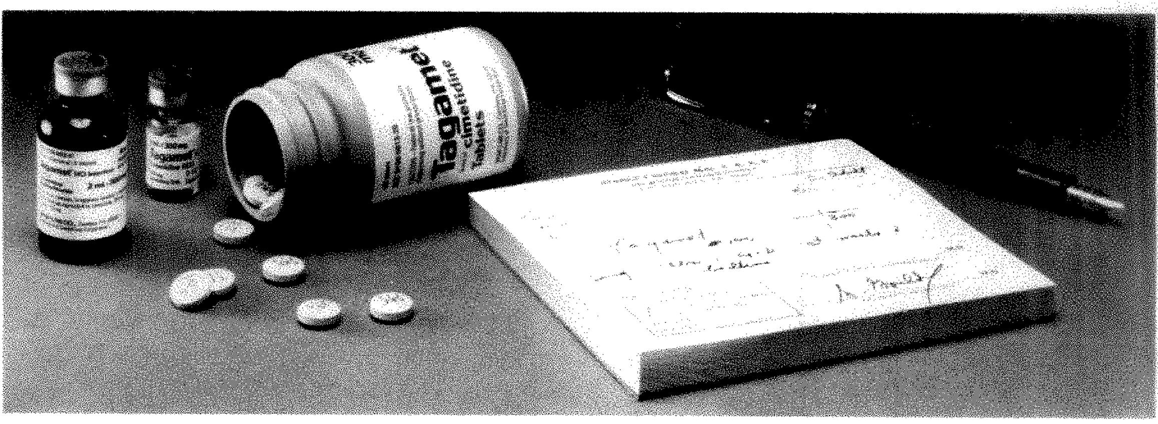

**Dosage in Duodenal Ulcer**

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

**Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.**

**Indications:** 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

**Contraindications:** There are no known contraindications to the use of 'Tagamet'.

**Precautions:** In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

In patients on warfarin-type anticoagulants, further prolongation of prothrombin times has been observed with concomitant 'Tagamet' administration. Close monitoring is recommended, and adjustment of the anticoagulant dose may be necessary.

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**References: 1.** Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

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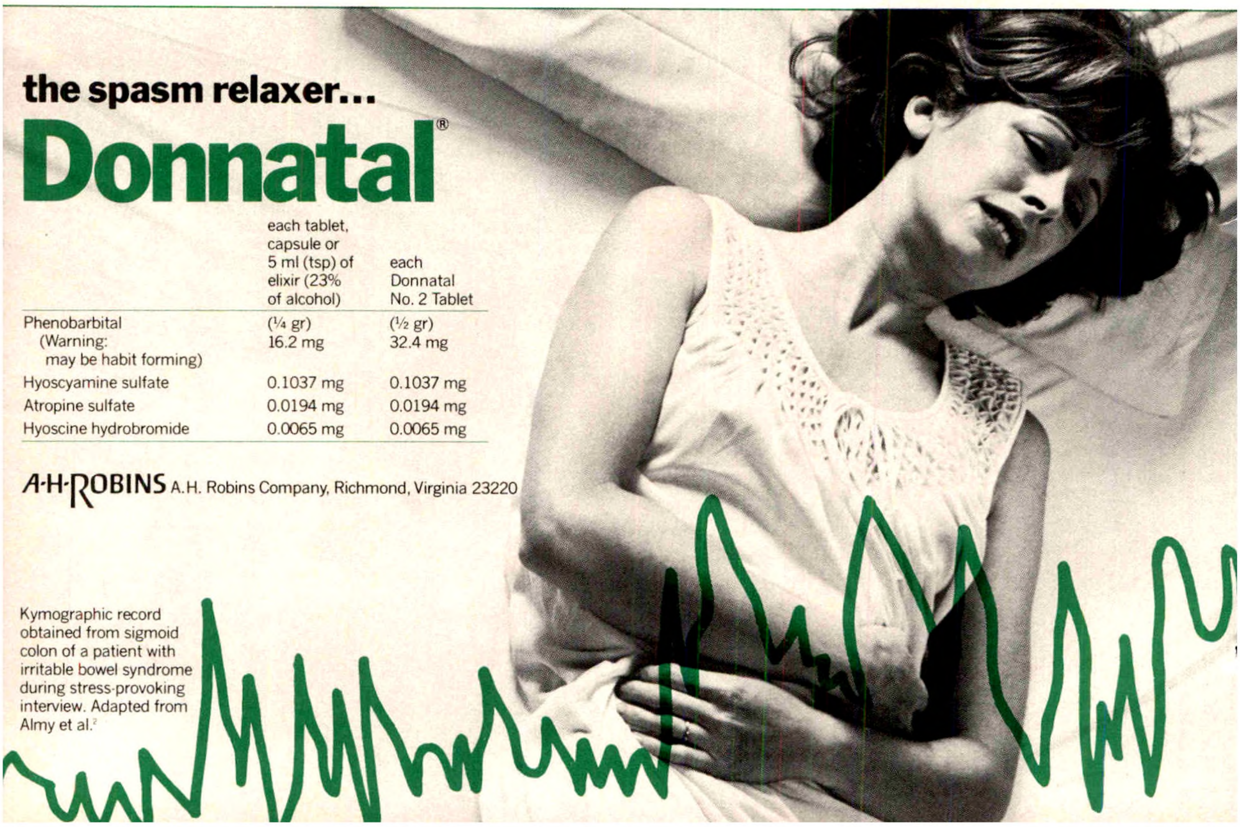

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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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# Cost Containment—Whose Business?*

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The problem of cost containment in medicine generally and gastroenterology in particular should be the number one concern of all of us who are practicing gastroenterologists. It certainly is to the health planners, the political analyst and the economist.

## Facts Pertaining to the Cost of Medical Care in General

Hospital costs are rising faster than the cost of living. If all costs had gone up the same as hospital care, we would be paying $13,000 for a small car, more than $1.00 for a package of chewing gum and $2.00 for a bottle of beer.

If a cure for cancer were found tomorrow and health care refused to introduce it because it was not cost effective, can you imagine what would happen?

Hospitals provide care for millions of people who cannot pay. The penniless consumer can be denied a 50¢ loaf of bread but not a $1,000 surgical procedure.

New technology may save labor in other industries but not in hospitals. They have to be run by men and women with special skills. In fact, today's hospitals have as many as 200 job classifications which didn't exist 20 years ago.

More than 70% of a hospital's budget goes to wage and employees' benefits. This is far higher than the percentage in industry as a whole.

A hospital job is not 40 hours a week. It is 24 hours a day, seven days a week. Because of this it takes five people to cover one job in the hospital.

The health care industry employs 5 million people, contributing 8.5% to our nation's gross national product.

One hundred forty million dollars was spent on the direct cost of medical care in this country last year. Forty billion dollars alone was spent on medicare and 50% of this $40 billion was spent on the last six weeks of life.

A total hip replacement cost $6,000; a coronary artery by-pass, $13,000; kidney dialysis, $1 billion, last year.

A recent national survey showed that 45% said they were not satisfied with the health care they received and 37% said they were somewhat satisfied; only 47% were dissatisfied completely. Fifty per cent of the public considers their cost of medical care "far too expensive" and another 22% considers it "somewhat expensive". Only 16% say their costs are about right and 8% say medical costs are a bargain. The latter group includes those who tend to be young, rich and insured.

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* Special lecture presented at the 43rd Annual Convention of the American College of Gastroenterology, Denver, CO, 27 September 1978.

† Board of Trustees, American College of Gastroenterology; Manager, Department of Health and Hospitals, City and County of Denver.

The major reason for the rise in the cost of hospital care is not a rise in prices in excess of inflation according to Nobel Prize winner, Milton Friedman but rather an increase in the number, variety and complexity of the procedures being used; tests that are being made and services that are rendered to patients. The cost of medical care has been going up because the public has *wanted* to buy more medical care and the market has been responding to their demands.

Costs have not been rising because hospitals are inefficient, even though they are but the hospitals haven't increased in their inefficiency to make the difference in costs.

The costs have not been rising because physicians are more greedy than they have been. All of us, physicians and lay people alike, are greedy. It is not this universal failing that causes costs to rise but rather there has been a pressure to expand services. Perhaps patients have been silly in regard to health and maybe they have wasted their money on annual physical examinations for reassurance. But, Dr. Friedman says, one of the freedoms of society is that they can make their own value judgments in what they want to be foolish when it comes to spending their own money.

## VIGNETTES THAT ILLUSTRATE SOME PERTINENT POINTS

When I was practicing at the Mayo Clinic, a patient came to me and said and this was in 1941, "You have a fine place here. Do all you want, but stop when it costs me $80." This never happened to me before and it never happened again. It didn't work then and it wouldn't work now. Because when it comes to one's own health, "money is no object". At the present time, it is obvious that the patient's single rule is to seek care at least up to the level of his insurance policy.

In our Denver General Hospital, a chronic alcoholic was admitted, because in a drunken stupor he fell downstairs and ruptured his bowel. Three months and $58,000 later he left the hospital cured, only to return two weeks later with about the same condition. All of this was paid out of general tax funds. Question—what is society's obligation to people who won't or can't help themselves?

For the next vignette I am indebted to my friend, Dr. Howard Hiatt, Dean of the Harvard School of Public Health.

He described a first year medical student who came into his office who asked, "How could we justify the expenditure of societies' resources for the care of the large number of elderly patients hospitalized for treatment of advanced degenerative diseases, when just a few minutes walking distance from the hospital, there were hundreds of children with inadequate housing and diet?" A prolonged discussion failed to alter her view of this as a gross inequity.

Two years later, the first day of her clerkship in medicine, Dr. Hiatt saw her emerge from a patient's room. Tears welled up in her eyes when she saw him. Her first patient was a man in his 80's, confused and paralyzed as a result of a stroke. This was her first personal exposure to the question she had posed two years earlier. The dilemma now arrived in a different shape. However deeply she felt about the inequities and the allocation of society's resources, as that patient's personal physician, she could only focus on what was best for him.

The physician, caught up in the demanding care of individual patients, has little time to step back and appreciate, much less change, the system.

The point of this story is: what are the individual's rights vs. society's rights?

An 80-year old man in a nursing home, very alert mentally, can't walk because of arthritis in both hips. Total hip replacement will alleviate this condition at a cost of $16,000, but he is 80 years of age!

Question—Who makes the decision to operate: the doctor, the patient, the family, or society?

A young woman with widespread cancer of the breast wants no more therapy but there is some available that might prolong her life—not cure her.

Question—Who makes the decision to stop therapy: the doctor, the patient, the family or society?

## PROBLEMS WHICH HAVE TO BE ADDRESSED

By using these examples, perhaps I have pointed out some of the problems which have to be addressed.

How can one cut costs if you can't cut services?

What is defined as basic medical care vs. abnormal medical care?

How much does government itself add to the cost of medical care? The government a few years ago had Hill-Burton funds to increase hospital beds and now they say we have too many beds.

What are the individual's rights vs. society's rights?

What are the value judgments—are some people of more value than others and who merits what?

The right to live and the right to die.

Do we have an ethical obligation to do everything that is technologically possible?

Who makes the decisions in all of this and what is the decision-making process.

Let us start with the last question as to who makes the decision in an analysis of what methods are actually available to us.

There are only three ways a decision-making process can be handled in this regard:

The democratic process. Have our pluralistic society decide by referendum if no other way.

An ethics committee that will make the decision for all.

The political process in which the government decides what should be done, which do you people want?

I submit as physicians we have a responsibility to lead wisely in this decision-making process.

## SOLUTIONS TO SOME OF THE PROBLEMS

*The questioning of rationing:*—It used to be that this was done in the market place. Those who could afford—got. This is one form of rationing. This should no longer be true. Society has decided that medicine is a right not a privilege. Third party payments are here to stay. Funds for those who are medically indigent are available and national health insurance is around the corner.

My only thesis as far as solutions are concerned is this. It is self-evident that hospitals are simply not going to cost less in the future. Are we going to throw out the present technology or the new technology of the future? The answer is no. Are we going to stop paying living wages to hospital help? The answer is no.

We must look to out of the hospital ambulatory care for the answer. And, in my opinion, this is our last chance to do something of a meaningful nature. How will the emphasis on ambulatory care help? Answer—this is the only foreseeable method of stopping the spiral of hospital costs. Only by keeping people out of hospitals and long-term facilities can a cost reduction be made. It is much cheaper to treat a patient by preventing the end stages of cirrhosis of the liver than by putting them in a hospital to treat the disease. It is well to remember that at the present time an inpatient hospital bed costs $430 per day counting everything and an outpatient hospital day costs $60 counting everything.

## Cost Containment as it Relates to Gastroenterology

When I started in gastroenterology as a sub-specialist, it was a new sub-specialty. As a matter of fact, I was the 123rd person to pass the sub-specialty boards in gastroenterology.

When I started practice I noticed the phenomenon. It is really still true. In certain quarters the general internist or family doctor would shyly ask me to do an endoscopy on a specific patient when what he really wanted was a gastroenterological consultation. It was less threatening for him to ask for a procedure but he truly appreciated the consultation that went with it.

I mentioned that I was one of the earliest sub-specialists in gastroenterology when I came back to Denver in 1945. At that time, there were two of us who were board certified. Now there are 34. It used to be that Denver was considered a regional center and difficult cases were referred from the outlying cities: Boulder, Greeley, Ft. Collins, Pueblo and Colorado Springs. Many of these same cities have surgeons who have become reasonably skilled with experience or because of attending courses in gastroscopy-colonoscopy. They also have their own trained gastroenterologists.

What is the reason for this increase? I would submit the following:

It is the training institutions that dictate the number of gastroenterologists. It is the institutions' needs and not really the needs of society. This could be elaborated in great detail.

How much has endoscopy taken over the practice of gastroenterology? The American Society of Gastrointestinal Endoscopy is larger now than the American College of Gastroenterology. What are the economics of endoscopy versus those of the consultation. I could spend two to three hours with a patient and get a minimal fee for an office visit or I could do an endoscopy which might take a fraction of the time of a consultation and be recompensed at a much greater level. It is truism that the sub-specialties of Internal Medicine that have grown the fastest are those which have procedures associated with them and consequently have elevated fee scales, i.e. cardiology, gastroenterology, nephrology.

Let us talk abut some of the problems of endoscopy. In a letter to the Editor of *Gastroenterology*, Dr. David Langdon of Spokane said the saturation in gastroenterology has arrived in that city because, "everyone in town has already been scoped once or twice."

In 1976, in his presidential address to the AGA, Dr. Fred Kern of Denver made the following statement: "It must be recognized, however, that we are in serious danger of becoming technicians rather than consultants and teachers. Our colleagues call upon us for our technical skills rather than our sage advice."

If he had stopped there, all would have applauded. But when he went on to say that in general endoscopy has not increased our understanding of disease and he questioned as to how often endoscopic procedures benefited our patient—this was another story. It was at this point that there was no meeting of the minds of gastroenterologists in general and Denver gastroenterologists in particular.

It does bring up an important point—how loose are the indications for endoscopy and other technologies and how does this growing list of "questionable" indications increase the cost of medical care in our specialty?

Let's take a case in point: esophageal motility.

From a tool of the physiological laboratory in the first half of the century, it has gradually intruded itself into the clinical realm. As soon as that happened, commercial interests started the ball rolling. The production and sales of "motility machines" were pushed by the manufacturer.

Hospital administrators were also concerned that they would be the last hospital in town with this dandy instrument and once it is in place it had to be amortized by using it more often.

Blue Cross and Blue Shield and governmental regulatory agencies started to investigate reimbursement procedures.

Granted there are three areas where motility is important, i.e. esophageal reflux, evaluation of chest pain and achalasia. Does this mean that all hospitals have to have a machine of this magnitude and how many procedures have to be done on patients with lesser indications?

Now let us discuss the cost of all the procedures we do.

In any other modality once the instrument is paid for the cost per procedure goes down. Does this happen in endoscopy? Hardly and I am sure a case can be made why it shouldn't when we talk with each other but certainly when we talk to health planners or health planners talk to us, it is difficult to convince them.

We can summarize the age of modern instrumentation by stating the following truisms.

It has increased the quality of care.

It is accompanied by less humanism in medicine.

It has increased the cost by raising the standard of care.

It has caused regulatory agencies to increase their regulations now and will more so in the future.

Another problem that has to do with our sub-specialty is manpower problem.

Alfred Bollet estimates that specialties increase the cost of medical care, increasing hospital expenditures, while family practitioners decrease the use of hospitals. Sixty per cent of American graduates are going into sub-specialty training, thus the ratio of 2:3:1 of general internists to specialists will become 1:1 by 1990.

Statistics show that sub-specialists see fewer patients per day, charge more, order more laboratory tests, use hospital facilities to a greater extent than other physicians.

I submit that perhaps the patients the sub-specialists see are sicker, do require more tests, use more physician time and without this expenditure they would be sicker longer, ultimately costing more.

There is no question that medical care would cost less if there were no endoscopy or liver biopsy just as it would if there were no x-ray machines and no operating rooms.

The unfortunate thing is that we have to tell this to the health planners. Their decisions are being made on inadequate or wrongly analyzed data. But there is enough truth in the fact that unnecessary procedures do increase the cost of medical care so that we are on the defensive. The truly unfortunate thing is that health planners are being trained faster than physicians. Ten thousand planners a year are being cranked out by the various schools.

Then we have the problem with our confrères, particularly some surgeons. I do not know what it is about Denver that attracts professionals who make outlandish statements. Dr. Ben Eiseman, Professor of Surgery at the University of Colorado School of Medicine, writing in the *Archives of Surgery* said recently and I quote:

"Internists and primary physicians have both economic and professional motives in wanting to work-up preoperatively and hang on postoperatively to a patient who has come to them for care. The patient with obstructive jaundice will serve as an example. The surgeon, if he is called at all during the preoperative period, must suffer in silence during the long hospitalization, the endless series of expensive and largely frivilous laboratory procedures. As the patient's hospital and laboratory bills rise, so does the justified fee for the internist's supervisions of the alleged scientific work-up. The surgeon characteristically waits in the wings to be called on only at the last minute when the decision for operation has been made between the internist and the patient."

With friends like these, who needs enemies.

The surgeons now see an area that they covet—endoscopy. Do away with the gastroenterologists. Let's take it all: and I submit ultimately without any peer review by the gastroenterologists before the patient goes to surgery, the cost of medical care will escalate.

## CONCLUSIONS TO BE DRAWN

I have presented problems both general and specific to the gastroenterologists, of the huge problem that is going to envelop us all and that is the cost of medical care. My plea to you is this:

Be aware of the problem, forewarned is forearmed.

Keep our specialty as one of being consultants, doctors, teachers and not just technicians.

Do something about regulating the number of gastroenterologists—not for selfish reasons but to be sure that there is no under utilization of special skills. A diversion of talent away from the primary care areas of internal medicine can be a waste of talent.

Institute strict peer review for endoscopic procedures before the planners do it for us. Be sure that indications are strict and that the cost per procedure is minimal rather than maximal.

Be sure that procedures involving the gastrointestinal tract are part of a gastroenterological work-up. The procedure is only as worthwhile as the gastroenterologist who perform it.

As a society of gastroenterologists, let us organize to do something, particularly to answer some of the questions. After all, the best defense is a good offense.

I submit that this organization of clinical gastroenterologists should take a leading position in finding available solutions to the more obvious problems. In that event we will be doing ourselves and society a needed service.

*Admin. Off.*
*Dept. of Health & Hosps.*
*W. Eighth Ave. & Cherokee St.*
*Denver, CO 80204*

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# Determination of the Lower Esophageal Sphincter Pressure in Patients Having a Nissen or Belsey Fundoplication*

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Grand Rapids, MI

Thirty patients were studied prospectively in evaluating the Nissen (28) and Belsey (2) fundoplication manometrically using the Kronsberg probe and Honeywell recorder. Twenty-eight patients in the Nissen fundoplication group had abnormally low LESP preoperatively and normal postoperative for one year with an average increase of 9 mm. Hg. They became asymptomatic and their esophageal mucosa became normal and remained normal endoscopically for three years. The only failures were two patients treated with the Belsey fundoplication. The gas bloat syndrome occurred in two patients and was relieved by esophageal dilatation. The Nissen fundoplication should be highly recommended as the surgical procedure of choice in the treatment of reflux esophagitis not responding to a medical program.

Numerous surgical procedures for esophageal hiatal hernias with reflux have been used.[1-5] Varying success has been claimed by the surgeon doing his particular procedure; yet symptoms may persist and anatomical recurrences occur. Because of dissatisfaction with surgical results, reevaluation of surgical procedures for hiatal hernia must be done prospectively. This report evaluates prospectively 30 patients with reflux esophagitis pre- and postoperatively for one year after having a Nissen (28) or Belsey (2) fundoplication.

## METHOD

The Honeywell recorder and Kronsberg (solid state) probe were used. The patients received no premedication. They all had been fasting for at least 12 hours. All patients were done in supine position. The Kronsberg probe has three transducers each separated by 5 cm. Each transducer opening is oriented radially different by 120 degrees. The probe was withdrawn from the stomach into the esophagus in 1 cm. increments at 10 second intervals.

For entry into the study, all had demonstrated by x-ray and endoscopy an esophageal hiatal hernia. All had esophagitis on observation and by biopsy. They had been on a medical program of dietary discretion, antacids seven times a day, and elevation of the head end of the bed for greater than two months. Only those continuing to have symptoms and documented persistent esophagitis were considered for surgery.

Routine laboratory data including CBC, screening profile, urinalysis, chest x-ray and ECG were normal. All had gastric analyses and serum gastrin determination.

Twenty patients had pH determination with the Beckman pH probe. Esophageal manometry was performed in all patients preoperatively. At six weeks, six months,

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[*] Read before the 42nd Annual Convention of the American College of Gastroenterology, New Orleans, LA, 24, 25, 26 October 1977.

[†] Associate Clinical Professor, Department of Medicine, Michigan State University College of Human Medicine, Blodgett Memorial Medical Center.

This study was supported by the Blodgett Hospital Research Fund.

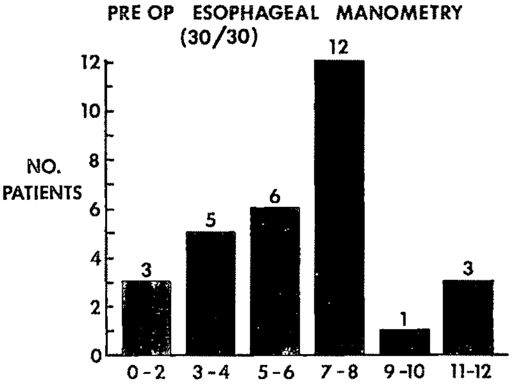

Fig. 1

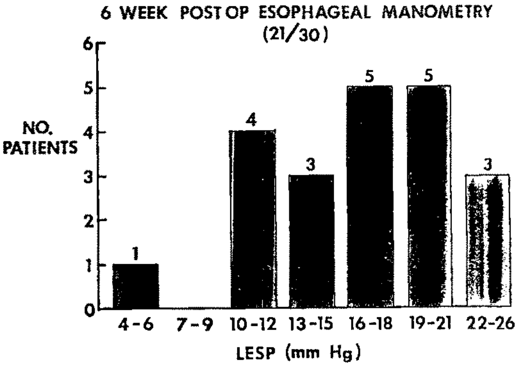

Fig. 2

and one-year follow-up recordings were made in the majority of patients.

There were 16 women and 14 men in the study with ages ranging from 16 to 68 and with an average age of 49. The range of normal in our laboratory for lower esophageal sphincter pressure is 12 to 28 mm. Hg.

## RESULTS

Preoperative lower esophageal sphincter pressure (LESP) was 9 mm. Hg. or less in 27 patients and 11, 11 and 12 mm. Hg. in the remaining three (Fig. 1). At six weeks, 21/30 patients were re-examined. They had increased their LESP by at least two times and all had values greater than 10 mm. Hg. (Fig. 2). One patient at six weeks and six months and another at six months were below 10 mm. Hg. (Figs. 2 and 3). They had the Belsey fundoplication and never improved their LESP nor were they symptomatically improved. Both patients had to be reoperated upon.

Twenty patients increased their LESP or stayed constant from the six-week postoperative LESP to the end of the one year evaluations. Eight patients decreased their LESP by 2 mm. Hg. or less at the end of one year (Fig. 4). An average increase of 9 mm. Hg. was achieved in the LESP of the 28 patients having the Nissen fundoplication.

Preoperatively, all patients had symptoms of heartburn, water brash and retrosternal discomfort. Twenty patients had dysphagia. Postoperatively, only the two patients having the Belsey operation had symptoms. After a three-year follow-up by history and endoscopy, no Nissen fundoplication patients had symptoms or esophagitis endoscopically.

Twenty patients had reflux preoperatively demonstrated by pH determination. Of 20 patients in the Nissen group, none had reflux at six weeks or six months.

Gastric analysis in 11/30 patients showed hypersecretion of hydrochloric acid on basal collection (greater than 40 mEq./l.). Eight had a vagotomy and pyloroplasty in addition to the Nissen fundoplication and three did not. The eight had an increase in the LESP of 8 mm. Hg. at six weeks postoperative and remained the same at one year. The three patients who did not have a vagotomy and pyloroplasty had an increase of 15 mm. Hg. in the LESP at six weeks and remained the same at one year.

Two patients experienced the "gas "bloat" syndrome. Two dilatations were re-

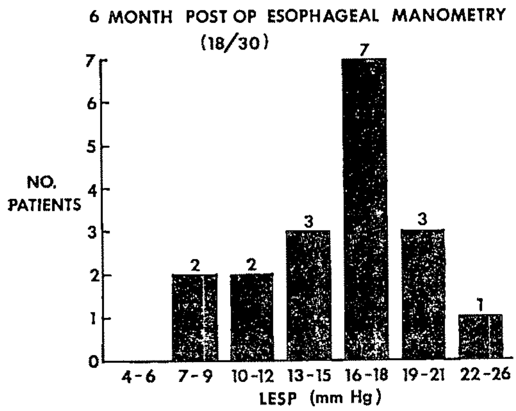

Fig. 3

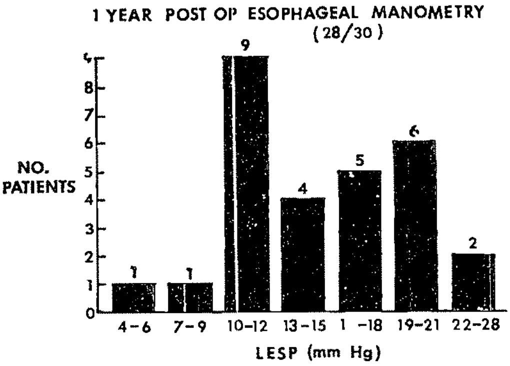

Fig. 4

quired to obtain relief. No patient in the Nissen fundoplication group experienced postoperative dysphagia. No motility disturbance was present preoperatively or postoperatively.

## COMMENT

Only a few prospective studies have been performed studying the results of the Nissen fundoplication in patients with an esophageal hiatal hernia and reflux esophagitis using pre- and postoperative manometry.[7-10] This prospective study took five years to complete. All of the patients having the Nissen fundoplication had relief of their symptoms. It was quite difficult to get them to return for periodic manometric and endoscopic evaluation because of their well being. The two patients having the Belsey fundoplication continued to be symptomatic and required further surgery.

An average increase in LESP of 9 mm. Hg. was achieved in the 28 patients in the Nissen group. This result is better than the result of Skinner and Booth,[8] who reported a 5.8 mm. Hg. mean postoperative pressure increase but less than that of DeMeester, et al[9] and Behar, et al[10] of 12 and 17 mm. Hg., respectively. This study's results are similar to those of Moran, et al.[11] Euler, et al[12] reported a mean increase in LESP in children having the Nissen fundoplication of 10.9 mm. Hg. using a perfused system. Kehrer, et al[13] reported a postoperative increase in LESP of 5-10 mm. Hg. in children using a nonperfused system.

Of the various technics used to surgically correct reflux esophagitis, the Nissen fundoplication is probably the operation associated with the lowest complication rate of 0.002% and the lowest recurrence rate of 8.25%.[14]

In contrast to the report of Woodward, et al[15] suggesting a high morbidity following the Nissen fundoplication due to the "gas bloat syndrome", only two of 28 patients in this study experienced this syndrome. Dysphagia secondary to the fundoplication operation did not occur postoperatively in this study as compared to the study of Bahadorzadeh and Jordan[16] and others. [9, 15]

Moran, et al[11] felt there was no correlation between LESP and the degree of symptoms and no correlation between postoperative LESP and the degree of relief of symptoms. This study disagrees with their results. All 28 of the Nissen fundoplication group had low LESP preoperatively and normal postoperative pressure. Their symptoms abated and no esophagitis was seen for three years as evaluated endoscopically. The only two patients remaining symptomatic in this study had low LESP pre- and postoperatively. Their esophagitis persisted clinically and endoscopically.

In this study, eight patients had a vagotomy and pyloroplasty for hypersecretion of hydrochloric acid in addition to a fundoplication. They had a lower increase in LESP than the three patients who had no vagotomy and pyloroplasty. Perhaps, parietal cell vagotomy without drainage as advocated by Bahadorzadeh and Jordan[16] should be considered for hypersecretors of hydrochloric acid especially with a previous history of peptic ulcer disease.

## ACKNOWLEDGMENTS

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***Communication from Abroad***

# Variable Premedication for Upper Gastrointestinal Endoscopy

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Seven regimens were employed as premedication for upper gastrointestinal endoscopy in 257 patients. Where possible the endoscopist remained unaware of the type of sedation given. Least anxiety was exhibited in the group receiving 2 mg. flunitrazepam (Rohypnol). Best sedation was achieved with both 1 and 2 mg. Rohypnol, diazepam and nitrous oxide. Easiest intubation was achieved in the group receiving neurolept analgesia, without topical analgesia and tolerance of the procedure was best in this group and those receiving nitrous oxide. Vital signs did not alter in any group other than those receiving neurolept analgesia, in which respiration fell only transitorily. Gastric peristalsis and the state of the pylorus were similar in all groups.

It is concluded that the use of either 2 mg. flunitrazepam (Rohypnol) with anticholinergic and topical analgesia, neurolept analgesia, or a 50% nitrous-oxide-oxygen mixture with topical analgesia have significant advantages over the diazepam regime with anticholinergic and topical analgesia, and the anticholinergic with topical analgesia alone regime. The use of 2 mg. flunitrazepam should replace 10 mg. diazepam for routine endoscopies. Neurolept analgesia or nitrous oxide-oxygen can be employed for anxious patients, often when other regimes have failed. An anesthetist should be available to provide assistance should the respiratory rate fall below 10/min. in case the patient may develop respiratory embarrassment. Where there are no recovery facilities or where patients wish to return to work, the 50% nitrous oxide-oxygen mixture is the regimen of choice because of the rapid recovery of the patients. Because of its long induction time, and because it necessitates the help of a second physician, the use of nitrous oxide will not be suitable for all endoscopy purposes.

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## INTRODUCTION

We have routinely used diazepam and topical analgesia, with an optional anticholinergic agent (propantheline) for upper gastrointestinal endoscopies. This approach is employed by others[1, 2] but has many disadvantages. The sedation provided is often not adequate[3] and there is an inordinately long recovery time, preventing return to work and driving of a motor vehicle. In an attempt to cater for differing needs of patients in a variety of types of endoscopy units, we have attempted to individualize the premedication given prior to the procedure. In addition to diazepam, we studied regimens employing flunitrazepam (Rohypnol) in two doses, neurolept analgesia with and without topical analgesia, a 50% nitrous oxide-oxygen mixture and propantheline with topical analgesia alone.

## PATIENTS AND METHODS

The following seven drug regimens were administered. Where possible, the endoscopist remained unaware of the type of sedation administered. Anxiety was assessed by the Hamilton Anxiety Scale.[4] Endoscopy was carried out in a slightly darkened room, allowing good observation of the patient's respiratory rate.

*Group 1:*—Thirty-one patients received intravenous diazepam (Valium 10 mg.) and intravenous propantheline bromide (pro-Banthine 30 mg.) unless contraindicated because of glaucoma or prostatic enlargement, plus topical analgesia (4% lignocaine hydrochloride 60-120 mg.).

*Group 2:*—Fifty patients received 1 mg. flunitrazepam (Rohypnol) with propantheline and topical analgesia as above.

*Group 3:*—Fifty patients received 2 mg. flunitrazepam (Rohypnol) with propantheline and topical analgesia as above.

TABLE I

PERCENTAGE OF PATIENTS WITH ANXIETY

| | 1 Diazepam propantheline topical analgesia | 2 1 mg. flunitrazepam propantheline topical analgesia | 3 2 mg. flunitrazepam propantheline topical analgesia | 4 Droperidol fentanyl | 5 Droperidol fentanyl topical analgesia | 6 Nitrous oxide oxygen topical analgesia | 7 Propantheline topical analgesia |
|---|---|---|---|---|---|---|---|
| Prior to drug | 51 | 46 | 54 | 41 | 49 | 79 | 50 |
| Prior to procedure | 36 | 24 | *12* | 17 | 44 | 32 | 72 |
| During procedure | 77 | 70 | 40 | 32 | 52 | 33 | 91 |
| 30 min. after | 43 | 58 | 92 | 62 | 61 | *0* | 23 |

Figures in italics represent Least Anxiety Groups.

*Group 4:*—Forty-one patients received intravenous neurolept analgesia in the form of droperidol (Inapsin), in a mean dose of 5 mg., followed five minutes later by fentanyl (Sublimaze) in a dose of 1-2 μg./kg. until the respiratory rate fell to between 10 and 12/min. and 30 mg. propantheline bromide.

*Group 5:*—Thirty-six patients received intravenous neurolept analgesia as above, plus topical analgesia as in Groups 1, 2 and 3.

*Group 6:*—Twenty patients were given topical analgesia followed by a 50% nitrous oxide-oxygen mixture delivered in a system which does not allow the delivery of nitrous oxide in a concentration greater than 70%. In this group it was obviously impossible to conceal the nature of the sedation from the endoscopist.

*Group 7:*—Thirty patients were given 30 mg. propantheline bromide intravenously and topical analgesia, without systemic analgesia.

## RESULTS

*Anxiety (Table I):*—Immediately after receiving the drug, significantly fewer patients with anxiety were found in all groups except those given pro-Banthine and topical analgesia alone. Least anxiety was shown by those who received 2 mg. flunitrazepam (Group 3). The least anxiety during the procedure (10 minutes) were those who received droperidol and fentanyl (Group 4) and those who received the nitrous oxide-oxygen mixture (Group 6).

*Sedation (Table II):*—Significant sedation was achieved in all groups except those given pro-Banthine and topical analgesia alone. Immediately after receiving the drug, prior to the procedure, the best sedation was achieved in Group 1 (diazepam, 90%), Group 2 (1 mg. flunitrazepam, 96%), Group 3 (2 mg. flunitrazepam, 98%) and Group 6 (nitrous oxide, 100%). During the procedure, the best sedation was found in those who received nitrous oxide (Group 6) and 2 mg. Rohypnol (Group 3).

*Ease of intubation:*—The droperidol-fentanyl group without topical analgesia (Group 4) were easiest to intubate (70% without hold-up). Easy intubation was achieved with almost equal frequency in all other groups (29-42%).

*Tolerance of procedure:*—Tolerance of the procedure was best in those receiving droperidol and fentanyl without topical analgesia (Group 4, 82%) and nitrous oxide (Group 6, 80%).

*Gastric peristalsis:*—No difference was found in any group.

*State of pylorus:*—No difference was found in any group.

*Memory of the procedure:*—Only the group given pro-Banthine and topical analgesia alone (Group 7) achieved a good recall of the procedure. There were no other differences.

*Willingness to repeat procedure:*—Only Group 7 (no systemic analgesia) had a majority of those unwilling to undergo a repeat procedure. The greatest acceptance of the suggestion of a repeat procedure was in Group 2 (1 mg. flunitrazepam) and Group 6 (nitrous oxide).

*Pulse rate:*—The pulse rate increased significantly in all groups except those receiving nitrous oxide (Group 6). The increase was greatest in Groups 1 (diazepam) and 7 (no systemic analgesia).

*Respiratory rate:*—The only significant change in respiratory rate was a fall in those receiving neurolept analgesia (Groups 4 and 5). The reduction in rate was reversed within the first 10 minutes of the procedure.

*Systolic blood pressure:*—A fall in systolic blood pressure occurred in all groups except in those receiving nitrous oxide (Group 6) in whom no change occurred and in those receiving pro-Banthine and topical analgesia alone (Group 7), in which an increase in respiratory rate occurred.

*Diastolic blood pressure:*—No change occurred in any group.

## COMMENT

The benzodiazepines are in constant use for gastrointestinal endoscopy.[1, 2, 5, 6] Diazepam (Valium) is the principal form used. Benzodiazepines have many advantages in endoscopy, chief of which is the promptness of onset of action. Their chief effect is a hypnotic reduction in anxiety.[6] A light sleep is induced with muscle relaxation, yet the patient is quite able to respond to commands. Benzodiazepines have little or no effect on the cardiovascular and respiratory system.[7] In our series the use of diazepam was associated with two disadvantages. Intense burning on intravenous administration occurred frequently, a point noted by others, especially if a small vein was used.[8] In addition, it was usually many hours before the patient was able to leave the hospital and patients could not return to work or drive a motor car. In a busy Endoscopy Unit, extensive recovery facilities are required for outpatients.

Lignocaine 4% acted promptly and well, and its effects lasted for about two hours. In the dosage used the toxic effects of ventricular fibrillation and cardiac arrest were not induced.

Propantheline (pro-Banthine) was used for its antimuscarine and ganglion blocking effects[7] and in dosages of 30 mg. or more

TABLE II

PERCENTAGE OF PATIENTS SEDATED

| | 1 Diazepam propantheline topical analgesia | 2 1 mg. flunitrazepam propantheline topical analgesia | 3 2 mg. flunitrazepam propantheline topical analgesia | 4 Droperidol fentanyl | 5 Droperidol fentanyl topical analgesia | 6 Nitrous oxide oxygen topical analgesia | 7 Propantheline topical analgesia |
|---|---|---|---|---|---|---|---|
| Prior to drug | 13 | 4 | 6 | 5 | 3 | 0 | 0 |
| Prior to procedure | *90* | *96* | *98* | 55 | *76* | *100* | 7 |
| During procedure | 67 | 78 | *98* | 67 | 73 | *100* | 0 |
| 30 min. after | 43 | 58 | *92* | 62 | 61 | 0 | 3 |

Figures in italics represent Best Sedated Groups.

it did not induce restlessness or paralyze respiration.

Flunitrazepam (Rohypnol) is a benzodiazepine derivative related to nitrazepam and diazepam and shares the latter's similar applications to anesthesia.[9] It has psychosedative, anticonvulsant and hypnotic properties and is available for oral administration or as a solution for intravenous use. It may be used as a premedicant for sedation during surgery under regional analgesia or as an induction agent. A slow rate of injection of about 1 mg. in 30 seconds is usual and consciousness is lost one-two minutes later. In 1-2% of patients induction has been reported to be difficult or impossible.[10] After sleep has been induced, reflexes are depressed or abolished and reaction to pain may be diminished, although the drug has no direct analgesic action. No cardiovascular or respiratory effects occur.[11] Less anxiety and better sedation occurs with 2 mg. flunitrazepam compared to diazepam.

In an attempt to improve sedation and lessen anxiety at the time of the procedure and to hasten the recovery after the procedure so as to allow return to work and the ability to drive a car, we have employed a 50% nitrous oxide-oxygen mixture. This is delivered in a system which will not permit the delivery of a concentration of nitrous oxide of greater than 70%. In addition, we employed 4% lignocaine hydrochloride as topical analgesia in this group. At the 50% concentration, relative analgesia is achieved. There is amnesia but the patient is able to respond to commands.[12] We found the 50% nitrous oxide-oxygen mixture, with topical analgesia, to be a safe and effective agent for gastrointestinal endoscopy. The disadvantage to a busy Endoscopy Unit is its relatively long induction time. Blood saturation is achieved in 10 minutes.[12] Its greatest advantage is the very quick return to full consciousness after cessation of the procedure.

Neurolept analgesia is induced by combining butyrophenones (droperidol, Inapsin) with short acting narcotics (Fentanyl, Sublimaze) or synthetic opioids. A state of ataraxia or calmness with a detached attitude results and immobility to external stimuli without inducing sleep occurs.[13] This neurolept analgesic state can be used for gastrointestinal endoscopy[3] and cystoscopy examinations, radiological studies and both minor and major surgical procedures with supplementation, can be carried out.[14] Pharyngeal reflexes are depressed allowing intubation without topical analgesia. This was not seen with the other regimens. Less anxiety and better sedation were achieved by neuroleptic analgesia compared to diazepam. We have recently employed this technic for many anxious patients who have been unruly or refractory to sedation with diazepam.

Droperidol (Inapsin) belongs to the butyrophenone group, which is closely related to the phenothiazines. They act on the membrane of neural cells[15] and the synapses. Permeability is altered, thereby blocking the action of dopamine, noradrenalin, 5-hydroxy tryptamine and y-amino butyric acid.[16] Droperidol has an antiemetic effect 700 times greater than chlorpromazine.[16] It is a major tranquilizer and has minor side-effects which include hallucinations, weightlessness, fall in blood pressure, bradycardia, respiratory depression and reduction in secretions. Hypothermia, antihistaminic activity and occasional dyskinetic movements occur. Its effects last for six to 12 hours before it is excreted in the urine and feces.[13] The dose of droperidol used in our series was 5 mg. intravenously. Side-effects were minimal in our series, probably because of the small dose utilized.

The analgesic fentanyl (Sublimaze) is closely related to pethidine chemically[17] but has morphine-like actions[18] with resultant relief of pain, sedation and smooth muscle constriction.[19] It may also induce ventilatory depression, emesis, constipation, histamine release and muscle rigidity[20] of the chest wall which reduces lung compliance.[21]

Fixed combination preparations such as Innovar[22] were not used in our series. Separate dosages with varying increments according to requirements were employed.

Used in varying combinations in our series, neurolept agents caused no cardiovascular depression, although care is advised in hypovolemic states.[13] They can be used safely in porphyria but caution should be exercised in patients with liver disease.[13]

The antidote to fentanyl, nalorphine (Narcan) 5-10 mg. intravenously, has immediate effects. It was required for one elderly patient for respiratory depression. An anesthetist should be available to provide assistance should the respiratory rate fall below 10/min., in case the patient may develop respiratory embarrassment.

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# Hepatitis B Antigen and Antibody in Heroin Users

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Hepatitis B surface antigen ($HB_sAg$) and antibody (anti-$HB_sAg$) were determined on 442 asymptomatic heroin users and 246 controls. Of the drug-taking group, 124 used heroin intravenously and 318 nonintravenously (smoking, sniffing). Twenty-three (5.2%) heroin users were $HB_sAg$ positive and 118 (26.7%) anti-$HB_sAg$ positive, compared to three (1.2%) $HB_sAg$ positive and 28 (11.4%) anti-$HB_sAg$ positive controls, both statistically significant. $HB_sAg$ was positive in eight (6.5%) intravenous heroin users and statistically identical to 15 (4.7%) $HB_sAg$ positive nonintravenous users. Positive anti-$HB_sAg$ in 55 (44.4%) intravenous heroin users compared to 63 (19.8%) nonintravenous users, however, is statistically significant.

## INTRODUCTION

Drug users are commonly exposed to Type B hepatitis, and as a result have a high incidence of that disease.[1-6] In addition, asymptomatic heroin users have an increased incidence of hepatitis B surface antigenemia ($HB_sAg$), which may be persistent, similar to that of persons transfused with blood.[4, 7-9] The mechanism underlying the presence and persistence of antigen are unknown but may be related to increased and repeated exposure, genetic factors, antigen dose, action of the abused drug or excipients, immunologic susceptibility, or some undetermined cause.

The purpose of this paper is to compare the incidence of hepatitis B antigen and antibody both within a unique group of drug abusers and to a group of matched controls.

## MATERIALS AND METHODS

Blood specimens were obtained from 442 male United States soldiers on admission to a United States Army, Republic of Vietnam (USARV) Drug Treatment Center. The heroin user demographics are summarized in Table I. The blood samples from controls were obtained from 246 male United States soldiers who denied heroin use and had no opiates in their urine by biochemical testing at the time their blood was taken. These individuals included medical technicians at the USARV Drug Treatment Center and other soldiers departing Vietnam upon completion of their tour. The

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TABLE I

HEROIN USER AND CONTROL DEMOGRAPHICS

| | Heroin users | | | Controls |
|---|---|---|---|---|
| | Total | Intravenous | Nonintravenous | |
| Number | 442 | 124 | 318 | 246 |
| Age, mean | 20.5 yr. | | | 23.8 yr. |
| Length of tour in RVN, mo. (mean) | | 9.1 | 9.0 | 8.1 |
| Duration of use of drug, mo. (mean) | | 9.1 | 7.6 | |
| Numbers of vials used per day (mean) | | 6.8 | 3.9 | |

One vial usually contained 200-300 mg. of essentially pure heroin.

control demographics are also summarized in Table I.

Serum specimens were assayed in duplicate for $HB_sAg$[10] and anti-$HB_s$[11] by solid phase radioimmune assay with reagents obtained from Abbott Laboratories (Austria and Ausab). $HB_sAg$ specificity was demonstrated by inhibition of the reaction with anti-$HB_s$ but not with normal guinea pig serum.

Results are reported as positive or negative and the totals in various groups compared using chi-square analysis. Differences between groups which might be expected to occur with less than a 5% likelihood of chance ($P < 0.05$) are considered significant.

## RESULTS

The numbers and percent of positive $HB_sAG$ in intravenous and nonintravenous heroin users compared to controls is shown in Table II and that of anti-$HB_s$ in Table. III. The prevalence of $HB_sAg$ in all heroin users was significantly greater than in controls ($P < 0.005$). Although intravenous users had a somewhat higher prevalence of $HB_sAg$ than nonintravenous users, the difference is not significant. Anti-$HB_s$ was found in significantly more heroin users than controls ($P < .005$). Anti-$HB_s$ was also significantly more frequent in the intravenous heroin-using group compared to the nonintravenous heroin users.

## COMMENT

The prevalence of $HB_sAG$ and anti-$HB_s$ among heroin users reported in the study is not surprising since the association has been observed and reported previously in a number of investigations.[4, 9, 12-14] In most of the prior reports, however, heroin was administered by the intravenous route and it was maintained that the use of contaminated equipment and materials and the sharing of this equipment with others, was responsible for the high incidence of hepatitis B and hepatitis B associated events in these populations.[6, 15] A single report has noted an increased frequency of $HB_sAg$ in nonparenteral drug users.[16]

TABLE II

$HB_sAG$ IN HEROIN USERS AND CONTROLS

| | $HB_sAg+$ | |
|---|---|---|
| | Number | % Pos. of group |
| Heroin users | 23 | 5.2 |
| Intravenous | 8 | 6.5 |
| Nonintravenous | 15 | 4.7 |
| Controls | 3 | 1.2 |

TABLE III

ANTI-$HB_S$ IN HEROIN USERS AND CONTROLS

| | Anti-$HB_s+$ | |
|---|---|---|
| | Number | % Pos. of group |
| Heroin users | 118 | 26.7 |
| Intravenous | 55 | 44.4 |
| Nonintravenous | 63 | 19.8 |
| Controls | 28 | 11.4 |

The present report is unique in that it provides data on a population that used heroin without intravenous injection and provides a comparison to subjects who used heroin intravenously as well as to a large number of nonusers. Nonparenteral use of heroin was possible in Vietnam because of the relatively high purity and low cost of the drug in comparison to other portions of the world.

The finding that the prevalence of $HB_sAg$ among nonintravenous heroin users did not differ significantly from intravenous users suggest that factors other than contaminated venipuncture played an important role in either the spread of hepatitis B or in promoting persistent antigenemia. Since it is known that $HB_sAg$ is spread by nonparenteral routes,[17, 18] a likely explanation is that both parenteral and nonparenteral users of heroin had more frequent, intimate contact with the indigenous population and each other, than did individuals in the control group and were therefore more likely to have been exposed to hepatitis B.

In contrast, antibody to hepatitis B among intravenous users was significantly greater than in nonintravenous users, suggesting that antibody formation was dependent upon antigen dose. An alternate explanation is that the intravenous using population had been on drugs for a longer time and thus had greater opportunity for exposure to antigen and production of antibody, compared to a shorter duration of exposure for the nonintravenous users. Since it takes approximately four months for antibody to be detected after exposure to $HB_sAg$[19] there could have been a considerable time lag during which only antigen and not antibody would be measured. This latter explanation, however, does not seem to be the case as response to our questioning indicates that the time of heroin use was approximately the same in both groups.

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# Ultrasound in the Diagnosis of Cholestatic Jaundice

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A total of 70 cases of cholestatic jaundice have been studied by gray scale ultrasonography in order to evaluate how this technic may be used to differentiate between intra- and extrahepatic cholestasis. In 37 out of 42 patients (88.1%) with jaundice of extrahepatic origin, dilatation of the biliary tree was demonstrated, whereas in all the 28 patients with intrahepatic cholestasis biliary dilatation was clearly excluded. In addition, gallstones in the biliary ducts were detected in 12 out of 20 cases and enlargement of the head of the pancreas (due to carcinoma or chronic pancreatitis) was often correctly diagnosed (nine out of 13 cases).

These results suggest that ultrasonography should represent the first step in the diagnostic approach to cholestasis. Information gained from this noninvasive technic should make it possible to correctly plan the more complex investigations (endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography).

Sonography has been used for some time to demonstrate dilatation of the gallbladder[1] and to detect gallstone formation[2-4] with a success rate varying between 60-90% depending on the number per series examined and the apparatus used. It has been very difficult, however, to visualize dilatation of the intrahepatic biliary tree, hepatic ducts and choledochus even though good results were obtained by Weill, et al[5] using "real time" equipment.

With the relatively recent introduction into clinical practice of gray scale equipment and with the aid of new scanning technics[6] identification of these structures is now rendered easier.[7-9]

A dilated gallbladder is always easily recognized by the vast oval-shaped echo-free area located at the right hypochondrium, often between the posterior surface of the liver and the right kidney (Fig. 1).

Gallstones of not less than 10 mm.[10] or, according to Crow, et al,[4] of not less than 3 mm., have the appearance of strong echogenic areas behind which an acoustic shadow, produced by the stone absorbing the ultrasonic beam, is almost always projected (Fig. 2). In some instances, for example if the stone is too small, or embedded in the gallbladder wall, or if there is not a sufficient quantity of liquid in the

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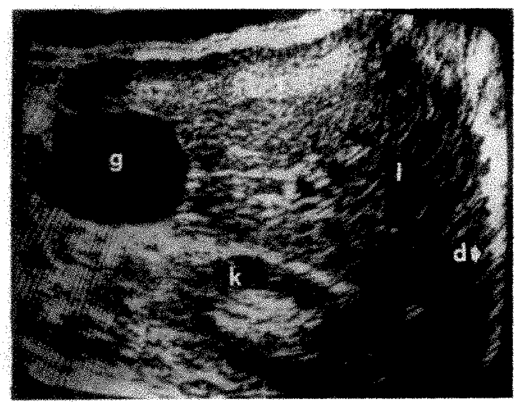

Fig. 1—Case 4, longitudinal section 4 cm. to the right of the mid line: marked dilatation of gallbladder. g = gallbladder; l = liver; k = right kidney; d = diaphragm.

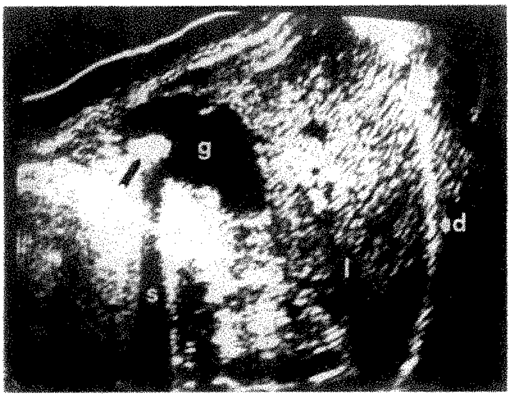

Fig. 2—Longitudinal section 3 cm. to the right of the mid line; cholecystolithiasis. arrow = stone; s = acoustic shadow.

gallbladder, diagnosis can only be based upon the presence of the acoustic shadow. In cases such as this it is sometimes difficult to distinguish cholecystolithiasis from choledocholithiasis. The diagnosis may be easier when dilatation of biliary radicles is visualized (Fig. 3).

The choledochus, visible only when dilated, has the appearance of an echo-free tubular structure located approximately parallel to the inferior vena cava and anterior to the portal vein (Fig. 4). In order to distinguish it from the portal vein, for which it may easily be mistaken,

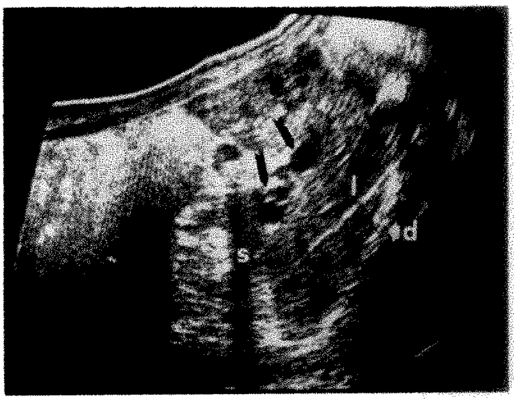

Fig. 3—Case 23, longitudinal section 3 cm. to the right of the mid line: an acoustic shadow(s) projected behind an irregular block of echoes indicative of stones is visible at the *porta hepatis;* dilated biliary ducts are clearly visualized (arrows). Surgery confirmed the presence of a choledocholithiasis in a cholecystectomized patient.

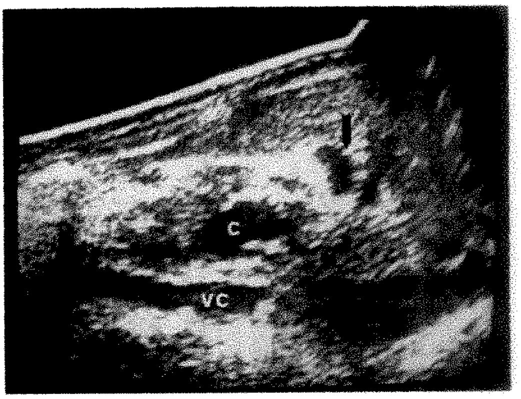

Fig. 4—Case 20, longitudinal section 2 cm. to the right of the mid line: dilated choledochus and biliary ducts (arrows). vc = vena cava; c = choledochus.

Weill, et al[5] emphasize the importance of using "real time" equipment.

Dilatation of the intrahepatic biliary tree is more readily recognized by the characteristic echo pattern—small roundish or channel-like echo-free spaces irregularly arranged in the parenchyma immediately adjacent to the *porta hepatis* are typical (Fig. 5). Taylor, et al[8] consider a star-like

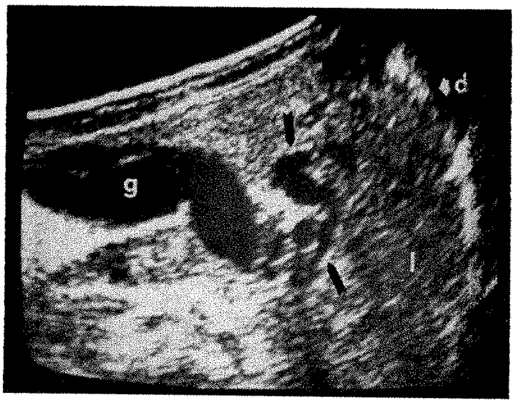

Fig. 5—Case 1, longitudinal section 4 cm. to the right of the mid line; marked dilatation of the gallbladder and biliary ducts (arrows).

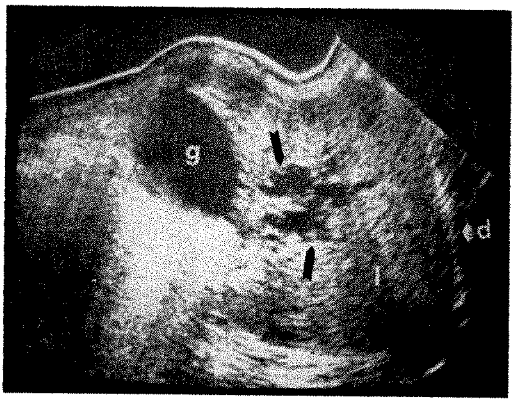

Fig. 6—Case 21, longitudinal section 3 cm. to the right of the mid line: star-like configuration of dilated biliary ducts (arrows).

configuration of dilated ducts in the region of the *porta hepatis* (visualized on a longitudinal scan taken at 3 cm. to the right of the mid line) to be a typical echo pattern of biliary tree obstruction (Fig. 6).

The present study was carried out in order to assess the value of ultrasonography in the differential diagnosis of extrahepatic cholestasis, in which dilatation of the biliary tree occurs above the obstruction, regardless of its site and nature and of intrahepatic cholestasis, i.e. pathological conditions of a hepatocellular, canalicular or ductal nature.

## MATERIAL AND METHODS

A Picker Echoview VI and an Aloka SSD 120 (both with gray scale equipment) were used for the investigations. A 2.25 MHz and sometimes, in case of thin subjects, a 3.5 MHz focused transducer was employed; the scanning technic was that described by Taylor and Hill.[6] A combination of sector and linear scan was used, particularly for longitudinal scanning which is more useful, in our opinion, for investigating the biliary system.

Forty-two patients (23 males and 19 females, ages 30-92 years, mean 66.7; duration of jaundice, 5-120 days, mean 33.6; total bilirubin, 1.5-50 mg.% ml., mean 11.3) with cholestasis of extrahepatic origin always confirmed at surgery or autopsy were selected for this study. Twenty of these patients were affected by choledocholithiasis, 11 by carcinoma of the pancreas, two by chronic pancreatitis, four by ampullary carcinoma, four by neoplasms of the biliary tract, one by metastatic lymphnodes at the *porta hepatis* (Table I). In addition 28 more patients with intrahepatic cholestasis were investigated for comparison. All patients were examined between June, 1976 and June, 1977.

## RESULTS

The major clinical and biological data, the surgical diagnosis, together with the ultrasonographic findings in the 42 patients with extrahepatic cholestasis are reported in Table I. In 37 of the 42 cases (88.1%) studied, even in those with partial or recent cholestasis. dilatation of the biliary tree (Figs. 5 and 6) above the *porta hepatis* was visualized. But if only cases with jaundice of over seven days and total bilirubin > 4 mg.% ml. are taken into consideration the percentage of cases correctly diagnosed rises to 93.1 (27 out of 29 cases).

TABLE I

ULTRASONOGRAPHIC FINDINGS IN 42 CASES OF EXTRAHEPATIC CHOLESTASIS

| Case | Age | Sex | Duration of jaundice (days) | Total bilirubin (mg.%ml.) | Dilated intrahepatic biliary ducts | Dilated choledochus | Distended gallbladder | Gallstones | Enlarged pancreas | Surgical or autoptic finding |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. R.F. | 46 | M | 120 | 2.4 | + | + | + | | | Ampullary carcinoma |
| 2. M.G. | 30 | F | 30 | 5 | + | | | + | | Choledocholithiasis |
| 3. E.G. | 73 | M | 20 | 18 | + | | + | | + | Pancreatic carcinoma |
| 4. B.E. | 52 | F | 20 | 5.6 | + | + | + | | + | Pancreatic carcinoma |
| 5. T.A. | 66 | M | 20 | 11.5 | + | + | | + | | Choledocholithiasis |
| 6. B.E. | 78 | F | 90 | 6.5 | + | + | | | | Choledocholithiasis |
| 7. F.R. | 60 | M | 30 | 3.2 | | | + | | + | Chronic pancreatitis |
| 8. T.C. | 62 | F | 10 | 6.2 | + | | + | | | Choledocholithiasis |
| 9. Z.O. | 71 | F | 15 | 19 | + | + | + | | | Carcinoma of the gallbladder infiltrating the common bile duct |
| 10. T.L. | 77 | F | 7 | 11.8 | + | | + | | | Pancreatic carcinoma |
| 11. P.F. | 54 | M | 60 | 2 | + | + | | | | Choledocholithiasis |
| 12. T.E. | 73 | M | 30 | 15 | + | | + | | + | Pancreatic carcinoma |
| 13. Z.G. | 32 | F | 60 | 7.7 | + | | + | | | Chronic pancreatitis |
| 14. G.D. | 55 | M | 30 | 50 | + | | | | | Carcinoma of the gallbladder infiltrating the choledochus |

TABLE I *(continued)*

ULTRASONOGRAPHIC FINDINGS IN 42 CASES OF EXTRAHEPATIC CHOLESTASIS

| Case | Age | Sex | Duration of jaundice (days) | Total bilirubin (mg.%ml.) | Dilated intrahepatic biliary ducts | Dilated choledochus | Distended gallbladder | Gallstones | Enlarged pancreas | Surgical or autoptic finding |
|---|---|---|---|---|---|---|---|---|---|---|
| 15. B.R. | 84 | M | 30 | 8 | + | | | | | Choledocholithiasis |
| 16. B.S. | 81 | F | 5 | 5.7 | | | | | | Choledocholithiasis |
| 17. B.D. | 63 | M | 15 | 1.5 | | | | | | Choledocholithiasis |
| 18. A.C. | 92 | F | 20 | 6 | + | | | | | Choledocholithiasis |
| 19. R.S. | 49 | M | 29 | 8.6 | + | | + | | + | Pancreatic carcinoma |
| 20. G.M. | 63 | F | 15 | 4.7 | + | + | + | | | Ampullary carcinoma |
| 21. G.A. | 86 | F | 18 | 12.5 | + | + | + | | + | Pancreatic carcinoma |
| 22. B.C. | 67 | F | 25 | 19 | + | | | | | Carcinoma of the gallbladder infiltrating the choledochus |
| 23. B.G. | 63 | M | 7 | 6 | + | | | + | | Choledocholithiasis |
| 24. G.M. | 75 | F | 8 | 1.5 | + | + | | + | | Choledocholithiasis |
| 25. V.D. | 65 | F | 30 | 8.6 | | | | | | Ampullary carcinoma |
| 26. R.L. | 80 | M | 11 | 2.2 | + | | | + | | Choledocholithiasis |
| 27. G.A. | 67 | F | 120 | 12.2 | + | + | + | | + | Pancreatic carcinoma |
| 28. P.R. | 77 | F | 25 | 11.2 | + | | + | | | Carcinoma of the choledochus |
| 29. C.S. | 87 | M | 60 | 12 | + | | + | + | | Choledocholithiasis |
| 30. C.L. | 54 | M | 20 | 30 | | | + | | | Pancreatic carcinoma |

TABLE I *(continued)*

ULTRASONOGRAPHIC FINDINGS IN 42 CASES OF EXTRAHEPATIC CHOLESTASIS

| Case | Age | Sex | Duration of jaundice (days) | Total bilirubin (mg.%ml.) | Dilated intrahepatic biliary ducts | Dilated choledochus | Distended gallbladder | Gallstones | Enlarged pancreas | Surgical or autoptic finding |
|---|---|---|---|---|---|---|---|---|---|---|
| 31. S.P. | 78 | M | 120 | 5.8 | + |  | + | + |  | Choledocholithiasis |
| 32. T.C. | 54 | M | 25 | 17.1 | + | + |  | + |  | Choledocholithiasis |
| 33. D.Q.R. | 69 | M | 15 | 6 | + | + |  |  | + | Pancreatic carcinoma |
| 34. L.S. | 75 | M | 12 | 10 | + |  | + |  |  | Pancreatic carcinoma |
| 35. B.N. | 86 | F | 30 | 24.3 | + |  |  |  |  | Metastatic lymphnodes at the *porta hepatitis* |
| 36. M.A. | 63 | M | 20 | 1.7 | + |  |  |  |  | Ampullary carcinoma |
| 37. M.A. | 69 | M | 40 | 19 | + | + | + | + |  | Choledocholithiasis |
| 38. G.B. | 61 | M | 20 | 34 | + |  | + |  |  | Choledocholithiasis |
| 39. F.G. | 64 | F | 30 | 16 | + |  |  | + |  | Choledocholithiasis |
| 40. B.N. | 68 | M | 30 | 15.6 | + |  | + |  | + | Pancreatic carcinoma |
| 41. B. | 54 | F | 14 | 5.2 | + |  |  | + |  | Choledocholithiasis |
| 42. M.A. | 77 | M | 10 | 6.4 | + | + |  | + |  | Choledocholithiasis |
| Number and percentage of cases exactly diagnosed in comparison with surgical or autoptic findings |  |  |  |  | 37/42 (88.1%) | 14/36 (38.9%) | 21/22 (95.5%) | 12/20 (60%) | 9/13 (69.23%) |  |

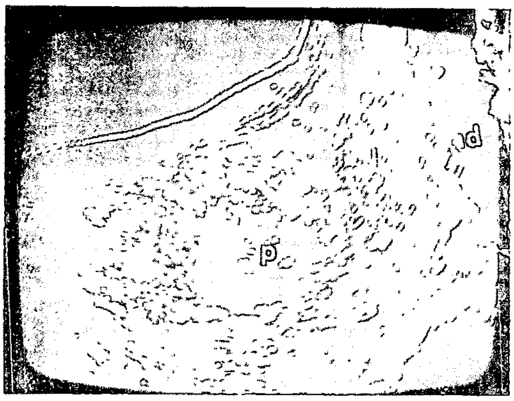

Fig. 7—Case 19, longitudinal section 1 cm. to the right of the mid line: marked enlargement of the head of the pancreas. p = pancreas.

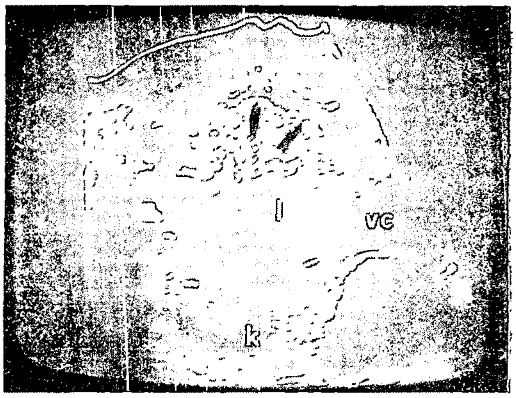

Fig. 8—Longitudinal section 3 cm. to the right of the mid line: dilatation of hepatic veins (arrows).

Dilatation of the choledochus (Fig. 4) was observed in only 14 out of 36 cases (38.9%). Ultrasonography showed choledocholithiasis (Fig. 3) to be responsible for cholestasis in 12 out of 20 cases (60%) and in eight out of 11 cases (72.7%) revealed the cause of cholestasis as being an enlargement of the head of the pancreas suggestive of cancer (Fig. 7),[11] as later confirmed at surgery. In one of the two cases of cholestasis due to chronic pancreatitis ultrasonography demonstrated the presence of a cyst in the head of the pancreas (ERCP had only furnished indirect signs) which was surgically proved to be responsible for the cholestasis. In the other case no enlargement of the head of the pancreas was found; there was nevertheless severe dilatation of the biliary tree.

Sonography was performed for control purposes in a further 28 patients with intrahepatic cholestasis. Dilatation of biliary ducts was not demonstrated in any of these cases. The investigation proved useful in some patients, however, in revealing evidence of liver metastasis or chronic liver stasis (dilatation of hepatic veins) (Fig. 8).

## Conclusion

Improved scanning technics and the introduction of gray scale equipment now render it possible to examine the liver anatomy in more detail and of particular importance to detect even slight dilatation of the biliary ducts and intrahepatic venous systems,[5, 7, 8, 12] thus adding a new dimension to the diagnostic approach in cholestatic jaundice, when traditional radiographic methods cannot be performed.

Employing the technic described, dilatation of biliary ducts can be detected without much difficulty. Dilated intrahepatic ducts are frequently recognized from the characteristic wending or star-like echo pattern. These structures are easily distinguished from the hepatic vein radicles which frequently interrupt the echogenic structure of normal liver tissue (Fig. 8). The latter are, in fact, more often found in the area below the diaphragm. They are usually isolated and increase in caliber the closer they come to the diaphragm. Of the portal venous structures the right portal branches are easily visible and are always surrounded by dense echoes thus providing a fairly characteristic echo pattern.[13] Identification of a dilated choledochus, on the other hand, is not always easy, probably on account of its oblique course from top to bottom and from front to back, making a complete longitudinal section in a single scanning difficult. In our opinion "real time" apparatus should be used in this case as it would also better distinguish it from the portal vein.

It is frequently possible to detect stones in the gallbladder or choledochus by ultrasonography. It is therefore of great assistance to identify the so-called acoustic shadows which are, for the most part, projected behind the stone formation.

The peculiarity of patterns obtained in extrahepatic cholestasis was confirmed by comparison with those obtained in 28 patients with intrahepatic cholestasis, in whom dilatation of the intrahepatic and extrahepatic biliary ducts was clearly excluded.

Therefore the importance of ultrasonography should be emphasized in the differential diagnosis of cholestasis due to extrahepatic biliary obstruction, which requires surgery, and intrahepatic cholestasis, which generally requires medical treatment. The finding of dilated intrahepatic ducts on ultrasound is always diagnostic (no false-positive results in 28 controls) but the absence of this findings cannot always exclude the presence of slightly dilated ducts, since five out of 42 cases without this finding on ultrasound had extrahepatic cholestasis. Because of our lack of experience, we consider a caliber of 8 mm. to be the minimum value of resolution.[9]

The advantages for the routine use of this technic in cholestatic jaundice are its complete innocuousness, the facility and rapidity with which it is performed and the possibility of repeat studies. Furthermore information gained from ultrasonography should make it possible to plan the more complex investigations needed for further clarification of the clinical picture. Thus, in our opinion, ultrasonography should represent the focal point in the diagnostic approach to cholestasis. In fact, since it is possible to distinguish with rapidity and precision (88.1% of cases presented in the present report and 97% of cases according to Taylor, et al[8] and 82% according to Mitchell, et al[12]) between intrahepatic and extrahepatic cholestasis, the choice of subsequent diagnostic investigations is facilitated. Either percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde pancreatic cholangiography (ERCP) may be considered taking into account their different characteristics and the information obtained from ultrasonographic studies.[14] PTC is the technic of choice when dilated ducts are clearly visualized. In this case, as Doust[15] reports, ultrasonograms can serve as a guide to PTC enabling it to be carried out with greater ease and precision. When no dilatation of the biliary system is found, or in case of enlargement of the head of the pancreas, ERCP should be performed.

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# Idiopathic Calcific Pancreatitis, CRST Syndrome and Progressive Systemic Sclerosis

## Report of a Case and Review of the Literature

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A 43-year old man with CRST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia) and progressive systemic sclerosis presented with a four-year history of relapsing abdominal pain, the result of chronic pancreatitis, not associated with alcoholism, biliary disease, or any of the known causes of pancreatitis. He had a good response to retrograde pancreatic duct drainage but exhibited management problems and complications that may be peculiar to the systemic sclerosis patient with pancreatitis. A cause and effect relationship between progressive systemic sclerosis and pancreatic disease is not proven but we believe there is evidence to suggest such a relationship.

The CRST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia) was first described as a clinical entity and associated with progressive systemic sclerosis (PSS) by Winterbauer in 1964.[1] Less than 5% of patients with PSS manifest the full syndrome.[2] In the first years following Winterbauer's description, CRST syndrome was felt to be a benign variant of PSS, seldom manifesting more than mild esophageal dysfunction in the way of visceral involvement.[3, 4] In more recent years, CRST syndrome has been associated with most, if not all of the various recognized visceral components of PSS and the presence of CRST syndrome does not signify a better prognosis in PSS.[2]

PSS involving skin, esophagus, lungs, kidney, heart and large and small blood vessels has been well documented in many series of both clinical and postmortem studies.[5-8] At least one large postmortem series[5] casts doubt on the possibility of pancreatic splenic or hepatic involvement in PSS but a more recent study[9] reports six cases of primary biliary cirrhosis in women with CRST syndrome. The association of diabetes mellitus in patients with PSS,[7] along with the relatively frequent findings of malabsorption, steatorrhea and deficiencies of pancreatic enzymes[10, 11] lend support to the possibility of pancreatic involvement in some patients with PSS.

We report a patient with CRST syndrome and apparent renal, splenic, pulmonary, cardiovascular and cutaneous manifestations of PSS who presented with abdominal pain caused by relapsing chronic calcific pancreatitis, not associated with alcoholism, malabsorption, hyperlipidemia, biliary disease, hyperparathyroidism, or other known causes of chronic pancreatitis.

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## CASE REPORT

A 43-year old white male was admitted to the Beth Israel Medical Center for evaluation of a four year history of recurrent, postprandial midepigastric abdominal pain, unresponsive to antacids and analgesics. He had a 10 kg. weight loss in the year prior to admission.

For at least 20 years he had been aware of discrete, red, macular spots on the palms of both hands, on the soles of his feet and on his lips and buccal mucosa. Fifteen years prior to admission, the patient had the first of many episodes of painful subcutaneous and intra-articular calcium deposits. At this time he first noted that exposure to cold air would cause his fingers to turn blue and become painful. Seven years prior to admission he was hospitalized for 15 days with a diagnosis of "subendocardial myocardial infarction" and had since suffered frequent but short episodes of precordial chest pain, for which he was taking isosorbide dinitrate, propranolol and nitroglycerin. Hypertension of five years' duration was managed with a combination of reserpine, hydralazine and hydrochlorothiazide. Other medications included clofibrate, diazepam and numerous narcotic and nonnarcotic analgesics.

The patient was a white-collar worker for a local utility, smoked two packs of cigarettes daily and denied more than infrequent social use of alcohol. His father, who had similar red spots and hypertension, died at age 62 of a myocardial infarction.

The patient was thin but not cachectic. Blood pressure was 140/100 mm. Hg.; pulse, 80/min. and regular; temperature 37° C. He had multiple, discrete telangiectases of mucous membranes, palms and soles and hard subcutaneous nodules of his forearms and fingers. The skin of the fingers and toes was hardened and thickened, the digits tapered distally and there was an hammertoe deformity of the feet. Examination of the heart and lungs was not remarkable. Peripheral pulses were uniformly palpable. The abdomen was soft, nontender and no masses or organs were palpated.

Admission hemogram, coagulation profile, stools for guaiac and urine analyses were normal. An erythrocyte sedimentation rate was 36 mm./hr. Daily serum amylase for the first week ranged from 199-756 I.U./l. (normal: 30-180). Serum lipase was 4.2 C.C.U./l. (normal: $< 1.5$). Serum electrolytes, fractionated proteins, lipoprotein electrophoresis, calcium, phosphorus, cholesterol, creatinine, bilirubin, alkaline phosphatase and liver enzymes were all within normal limits. Roentgenograms of the chest showed prominent interstitial markings.

A barium swallow and esophageal motility studies demonstrated diminished esophageal contractility. Roentgenograms of the hands showed overlapping phalanges and subcutaneous calcium deposits. Pulmonary function studies revealed normal lung volumes but the diffusion capacity was less than 50% of predicted value.

The upper gastrointestinal series showed a widened duodenal sweep and multiple calcifications in the region of the head of the pancreas (Fig. 1). Oral cholecystogram was normal. Sonography confirmed the presence of a mass in the region of the pancreas. An oral glucose tolerance test disclosed a diabetogenic curve at two and three hours. A secretin test revealed a markedly diminished total volume and bicarbonate concentration. Fiberoptic endoscopy of the upper gastrointestinal tract was normal but endoscopic retrograde cannulation of the pancreatic duct with fluoroscopically directed injection of contrast medium revealed marked stenosis of the main pan-

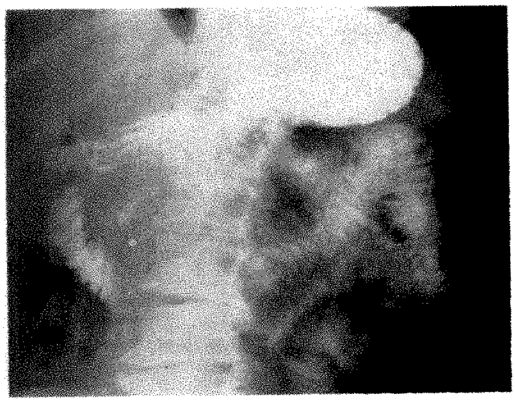

Fig. 1—Upper gastriintestinal contrast study showing widened duodenal sweep and multiple pancreatic calcifications.

creatic duct at the confluence of head and body (Fig. 2).

Selective splenic arteriography showed an enlarged spleen and a completely obstructed splenic vein. The catheter was withdrawn into the celiac axis and advanced into the common hepatic artery, but failure of blood return prompted withdrawal again into the celiac trunk. There, a few mililiters of contrast medium were injected, demonstrating a dissection within the wall of the celiac axis. The patient complained of sudden onset of excruciating epigastric and right upper quadrant abdominal pain. A flush aortogram showed complete occlusion of the celiac axis and no distal reconstitution, despite a widely patent superior mesenteric artery.

Within 30 minutes, an emergency laparotomy was begun. The liver was dark blue and shrunken. The common hepatic artery was completely thrombosed and a dissection between adventitia and media from celiac trunk to mid common hepatic artery was noted. An autologous saphenous vein graft was interposed between the aorta and the distal common hepatic artery and immediately the liver became dark red and more turgid. The gallbladder, previously pallid, was well perfused, appeared normal and

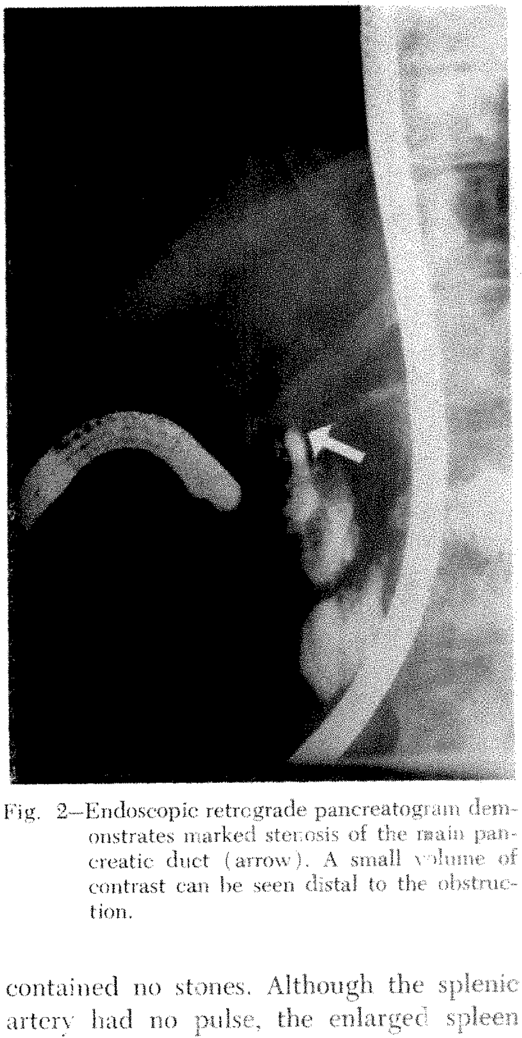

Fig. 2—Endoscopic retrograde pancreatogram demonstrates marked stenosis of the main pancreatic duct (arrow). A small volume of contrast can be seen distal to the obstruction.

contained no stones. Although the splenic artery had no pulse, the enlarged spleen appeared well perfused. The stomach and duodenum were grossly normal. The pancreas was enlarged, hard and nodular. The procedure was well tolerated. The postoperative course was complicated by transient hypertension, hyperglycemia and mental confusion. Liver enzymes, moderately elevated in the early postoperative period, were within normal limits after two weeks.

The patient continued to have severe epigastric pain, now associated with increasing episodes of retrosternal pain resembling angina pectoris. Amylase levels were consistently elevated. A left heart catheterization with coronary arteriography and left ventriculography demonstrated marked concentric left ventricular hypertrophy, mild pulmonary hypertension but normal coronary arteries. Abdominal aortography showed the aortohepatic artery graft to be patent.

With a preoperative diagnosis of chronic, relapsing pancreatitis, the patient was re-operated. At laparotomy, the pancreas was again noted to be diffusely enlarged, indurated and nodular. The pancreas was incised longitudinally and the main pancreatic duct was entered and probed proximally until a stricture was encountered, through which even the smallest Bakes dilator would not pass. There were multiple strictures in the main duct distally. The jejunum was divided at a point approximately 30 cm. distal to the ligament of Treitz. The proximal limb was anastomosed end-to-side to more distal jejunum. Roux-en-Y fashion. The defunctionalized limb of jejunum was anastamosed end-to-side to the main pancreatic duct, creating a longitudinal pancreaticojejunostomy (after Puestow and others[12-16]). The lesser sac was drained and the abdominal wall closed.

Multiple biopsy specimens of the pancreas were reported as "fibrosis and chronic inflammation".

The postoperative course was complicated by a pancreaticocutaneous fistula which appeared on the eighth postoperative day. Oral feedings were discontinued and total parenteral nutrition instituted. After 37 days the drainage ceased and the tract closed. The patient gained weight during this time and was pain-free. Postoperative serum amylase levels fell to and remained normal.

The patient was discharged nine weeks after pancreaticojejunostomy, tolerating a regular diet, with little or no discomfort and taking only antihypertensive medications.

## COMMENT

A causal relationship between progressive systemic sclerosis (PSS) and chronic calcific pancreatitis (CCP) has not been established. Diabetes mellitus and diminished pancreatic exocrine function in PSS, however, have been previously reported.[7, 10, 11] Pancreatic fibrosis was noted at autopsy in 17% of 58 patients with PSS reported by D'Angelo, et al,[5] although this did not represent a significant difference when compared to a group of matched controls without PSS studied by the same group. There is no indication, however, as to what percentage of "matched controls" were chronic alcoholics in this group drawn from the records of deceased patients undergoing autopsy at Baltimore municipal hospitals. Maingot places the incidence of chronic pancreatitis in the general population at about 0.5%.[17]

Vascular lesions are the *sine qua non* of PSS and a number of researchers believe that PSS should be classified as a vascular disease, with the primary site of injury at the microvascular level.[8] Involvement of larger vessels, when it occurs in PSS, probably results from initial involvement of *vasa vasorum*. Leinwand, et al,[18] describe acute arteritis involving all three layers of vessels and intimal proliferation with various degrees of obliteration of the lumen. Raynaud's phenomenon was one of the earliest described features of PSS.[19] The possibility exists that a diseased celiac axis contributed to the angiographic complication and future investigators are urged to exercise caution in the use of this modality in their patients with PSS.

The presence of pulmonary hypertension secondary to diffuse interstitial fibrosis was well documented in this patient and is the characteristic pulmonary lesion in PSS, occurring in 25 to 40% of cases.[4-7, 20]

Significant renal disease was present in 58% of D'Angelo's[5] patients with PSS, compared to 8.9% of controls ($p < 0.001$). Half of these patients were hypertensive at the time of their deaths.

The incidence of myocardial fibrosis among D'Angelo's[5] patients with PSS was significantly higher than amongst controls, especially when adjusted for age but interestingly and as in this case, coronary artery disease is not a feature of PSS. Early chronic congestive heart failure is frequent in PSS and can be related to associated systemic and pulmonary hypertension as well as myocardial fibrosis.[6]

The patient's father was also hypertensive and had palmar and mucosal telangiectasia. Although he had none of the other manifestations of CRST syndrome or PSS, an association between CRST syndrome and Rendu-Osler-Weber syndrome has been noted.[9]

To the best of our knowledge, the simultaneous occurrence of CRST syndrome, progressive systemic sclerosis and chronic calcific pancreatitis has not previously been reported and, in fact, pancreatic involvement in progressive systemic sclerosis is widely believed not to occur. We suggest that it does occur and that chronic pancreatitis be considered in the differential diagnosis of abdominal pain in patients with systemic sclerosis, even in the absence of alcoholism or biliary disease.

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*Communication from Abroad*

# Pancreatic Polypeptide (PP) Responses to Oral and Intravenous Glucose in Man

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Serum human pancreatic polypeptide (hPP) responses to 50 gm. of oral glucose and a 25 gm. intravenous bolus of glucose were measured in 10 healthy human volunteers. Oral glucose caused a 50% rise, whereas I.V. glucose caused a 35% fall in hPP concentration. There was no relationship between the absolute glucose concentration or the change in glucose level and the PP concentration. It is suggested that oral and I.V. glucose affect PP by indirect mechanisms and that PP may be involved in carbohydrate metabolism in man.

## INTRODUCTION

In dogs the known actions of bovine pancreatic polypeptide (PP) are directed at the pancreas, gut and gallbladder.[1] Avian PP stimulates proventricular secretion in the chicken but in addition depletes the chicken liver of glycogen.[2] The marked changes in PP concentration in man following ingestion of glucose[3] and insulin-hypoglycemia[4] suggest some relationship between PP and carbohydrate metabolism. No such metabolic actions have been demonstrated, however, for human PP (hPP) in man. To discover a possible role for PP in glucose homeostasis in man, hPP responses to oral and intravenous glucose tolerance tests were studied in 10 normal human volunteers.

## METHODS

The study protocol was approved by the Hospital Ethics Committee. Ten normal volunteers consented to have an oral (50 gm.) and an intravenous (25 gm. over two minutes) glucose tolerance test. The tests were performed in random order on two separate occasions after overnight fasting. Eight patients were male. They were all within normal weight for height range (Geigy tables), none was diabetic or on any medication and all signed informed consent. Blood was sampled from an indwelling catheter which was inserted into an antecubital vein and was kept patent by a slow infusion of saline. Two basal samples were taken at an interval of 15 minutes and after oral glucose administration blood was collected at 30, 60 and 90 minutes, while after I.V. glucose, blood was sampled at 3, 6, 10, 20, 30 and 60 min-

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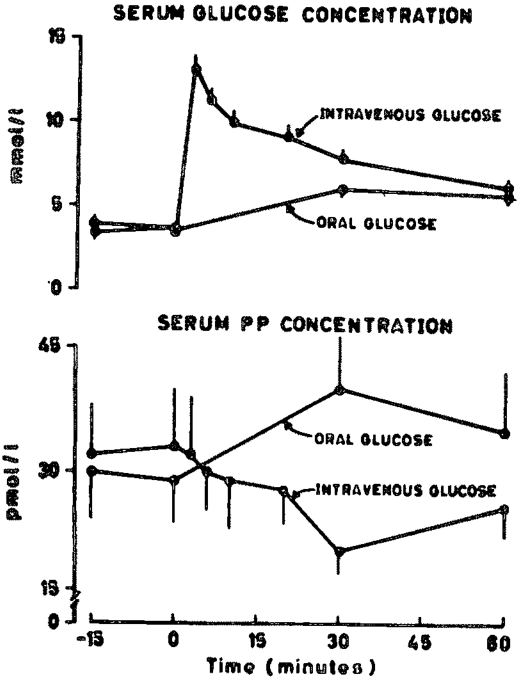

Fig. 1—Mean (± SEM) serum glucose and hPP concentration in 10 normal individuals after 50 gm. of oral and 25 gm. intravenous bolus of glucose given at time zero.

utes. The blood was allowed to clot, the serum separated by centrifugation and stored at −20° C until glucose was estimated by autoanalyzer using the ferricyanide method[5] and hPP measured by radioimmunoassay using rabbit hPP antiserum, hPP as standard and BPP for iodination, all kindly donated by Dr. R. E. Chance (Eli Lilly & Co.).

The results are presented as mean ± SE and the data were analyzed for significant differences using the paired "t" test.

## Results

Mean basal serum glucose concentrations were similar in both tests (3.6 ± .22 and 3.6 ± .13 mmol./l.). Glucose tolerance was normal in all patients by the criteria of Jackson and Vinik.[6] After intravenous glucose, peak glucose concentration of 13.3 ± .77 mmol./l. was recorded at three minutes and then plasma glucose fell over the next hour to 6.2 ± .47 mmol./l. at 60 minutes. With oral glucose, the peak glucose concentration was 5.9 ± .45 mmol./l. at 30 minutes and this fell to 5.1 ± .22 mmol./l. at 90 minutes.

Mean basal hPP concentration was 29.3 ± 5.07 pmol./l. before oral glucose and 33.2 ± 7.33 pmol./l. before intravenous glucose. The values were not significantly different. Thirty minutes after oral glucose, the mean plasma PP concentration rose significantly ($P = .02$) to 39.8 ± 6.29 pmol./l. With intravenous glucose, a slow steady fall in plasma PP concentration was observed to a nadir of 20.7 ± 2.62 pmol./l. at 30 minutes which was significantly ($P = .04$) below the basal concentration (Fig. 1).

## Comment

Oral glucose caused a significant rise in PP concentration. This confirms the observation of Floyd, et al[3] who found a small rise in hPP at 30 minutes but a much greater late response at 240 minutes. As we only sampled for 90 minutes, a further late response cannot be ruled out. The effect of intravenous glucose on plasma PP concentration is less clear. We observed a significant fall in the plasma PP concentration but this is contrary to the findings of Adrian, et al[4] who reported no change in plasma PP concentration for 60 minutes when 20 gm. of glucose was infused over 30 minutes. These observations are not really comparable to ours since we administered a single dose of 25 gm. of glucose as a bolus. To clarify this discrepancy further studies using similar protocols would be necessary.

The changes in plasma PP concentration did not relate to either the absolute level or the change in blood glucose concentration. Therefore, another indirect mechanism may be responsible for the PP changes found. Oral glucose may act via a gut factor to cause PP release. Secretin has been shown to stimulate PP release[4] but secretin is not released after oral glucose ingestion.[7] Other gut hormones may be involved in this process but as yet there is no data for or against this hypothesis. That vagotomy abolishes the PP response to feeding[8] does not exclude a hormonal mechanism since the vagus could release gut hormones directly (peptidergic) or via an action on gut cells. Gastric distention, following oral glucose ingestion, may activate the vagus and may have been responsible for the release of PP. This may be in keeping with the fall in PP following intravenous glucose, the stimulus of gastric distention overriding the glucose effect at 30 minutes.

Intravenous glucose depressed PP concentration. This could be due to decreased release, decreased pancreatic blood flow, increased inactivation of PP or mediated indirectly by the release of somatostatin. Glucose has no effect on PP release from the isolated perfused dog pancreas.[9] Although oral and I.V. glucose alter pancreatic blood flow, this does not appear to coincide with hormone release.[10, 11] There is no data on the effects of glucose on t½ of PP. Intravenous glucose, however, does decrease pancreatic effluent protein (enzymes) concentration[12] and has been shown to stimulate portal somatostatin release,[13] suggesting that an indirect hormonal mechnism may be involved.

hPP as another pancreatic hormone has not yet been shown to affect glucose homeostasis in man but the control of release appears to be related to the administration of glucose. Whether this relationship implies a role for PP in glucose metabolism or is consequent upon the secondary effects of acute changes in blood glucose levels requires further study.

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# Pancreatic Ascites

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Ascites occurring in patients with a history of alcoholism is usually due to cirrhosis but clinically significant ascites also occurs in association with pancreatic disease. We reviewed 265 cases of pancreatitis over a five-year period. There were 129 blacks and 136 Caucasians. Ages ranged from 19-86 years with a mean of 46.2 years. Eight of these cases (3%) were found to have pancreatic ascites. The initial serum and urinary amylase had no prognostic value regarding the subsequent development of pancreatic ascites. The mean ascitic fluid amylase was 14,426 Somogyi units (range 1,279-67,774). The mean ascitic fluid protein was 4.6 gm./100 ml. (range 1.4-7.2). High enzyme and protein concentration in the ascitic fluid are characteristic of pancreatic ascites. Out of eight cases, two were associated with a pseudocyst, three with hemorrhagic pancreatitis and three with acute edematous pancreatitis. Four of these eight (50%) died. Pancreatic ascites is a distinct clinical entity which should be differentiated from cirrhotic, tuberculous or malignant ascites.

## INTRODUCTION

Ascites occurring in patients with a history of alcohol ingestion is usually due to cirrhosis but clinically significant ascites also occurs in association with pancreatic disease.[1-15] In cases of acute pancreatitis, small amounts of peritoneal fluid are seen as a result of chemical peritonitis.[16-20] Patients with pancreatic carcinoma may develop ascites either due to peritoneal metastases or due to obstruction of the portal vein by the tumor.[19, 21-26] Pancreatic ascites refers to the accummulation of massive enzyme-rich ascitic fluid in cases of pancreatitis associated with pancreatic ductal rupture or pancreatic pseudocyst.[4, 27-52]

Eight cases of pancreatic ascites were seen in our institutions over a five-year period between 1971 and 1975. We have based our discussion on these eight cases. Pancreatic ascites seems to be a distinct clinical entity; the ascitic fluid contains very high concentrations of amylase and protein. Recognition of this entity is important. This condition should be differentiated from cirrhotic ascites, tuberculous peritonitis or peritoneal carcinomatosis, otherwise patients will fail to receive appropriate medical and surgical treatment.

## PATIENTS AND METHODS

The charts of patients admitted between 1971-1975 to the Louisville Veterans Administration Hospital and the Louisville General Hospital with a diagnosis of pancreatitis were reviewed. There were 265 cases of pancreatitis, 224 men and 41 women. There were 129 blacks and 136 Caucasians. Age ranged from 19-86 years with a mean of 46.2 years. Eight of these cases (3%) were found to have pancreatic ascites. The mean initial serum amylase in patients with pancreatic ascites was 595 compared to the rest of the group, 743 units (normal 60-160). The initial serum amylase seems to have no prognostic value regarding the subsequent development of pancreatic ascites. Similarly initial urinary amylase values, 1,976 u./hr. vs. 1,205 u./hr. were unhelpful in predicting the subsequent development of pancreatic ascites ($p > .005$). The mean ascitic fluid amylase was 14,426 units (range 1,279-67,774). The mean ascitic fluid protein was 4.6 gm./100 ml. (range 1.4-7.2). High enzyme and protein concentration in the ascitic fluid are characteristic of pancreatic ascites[1, 4, 14]

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## CASE REPORTS

*Case 1:*—M. L. H., a 33-year old black woman with a history of alcoholism was admitted with symptoms of abdominal pain, nausea and vomiting but no hematemesis. She had a past history of alcoholic gastritis. The abdominal pain was knife-like and radiated to the back. On examination she was in obvious distress with no physical stigmas of cirrhosis. Her abdomen was distended with marked epigastric tenderness. Shifting dullness and fluid thrill were present. Vital signs were normal. BUN, creatinine and serum electrolytes were normal. Serum calcium, 8.6; blood sugar, 98; total protein, 5.3; albumin, 1.6. Alkaline phosphatase, 18.3; Hgb., 10.9; Hct., 32.9; WBC, 13,400; differential was normal. Serum amylase was 705 units (normal 60-160); urinary amylase was 900 u./hr. (normal up to 400 u./hr.) She developed left pleural effusion. Plain film of the abdomen showed massive ascites with a positive sentinel loop sign. Abdominal paracentesis was performed and 7,300 cc. of straw-colored fluid was removed. The patient became hypotensive but responded to intravenous fluid replacement. Ascitic fluid amylase was 4,888 units; protein was 7.2 gm./100 ml. The patient was treated with nasogastric suction and analgesics and she continued to improve. Over a period of three weeks, the ascites gradually disappeared, the abdomen became soft and serum and urinary amylase returned to normal. Later an oral cholecystogram showed a normal gallbladder. At the time of discharge there was no ascites; serum amylase was 123; total protein was 8.3; albumin, 3.5; total bilirubin, 0.5; SGOT, SGPT and alkaline phosphatase were normal.

*Comment:*—A case of pancreatic ascites which responded to medical treatment.

*Case 2:*—H. L. B., a 62-year old white woman with a previous history of chronic cholecystitis and previous episodes of acute pancreatitis was admitted because of abdominal and back pain of three days' duration. On examination she had mild epigastric tenderness with a cystic mass. Serum amylase was 440 units; urinary amylase was 1,000 u./hr. Hgb. was 10.2; Hct., 32 BUN, 6.5; creatinine, 0.7; WBC, 8,300 with a normal differential. Total bilirubin was 0.45 with a direct bilirubin of 0.2. Total protein was 7.3 with albumin 3.3, alkaline phosphatase, 8.9. Upper gastrointestinal series showed medial displacement of the stomach. She developed left pleural effusion; amylase on pleural fluid was 28,000 u./100 ml. She continued to have abdominal pain. On laparotomy there were gallstones and the gallbladder showed evidence of chronic inflammation. A moderately large pseudocyst was found in the body of the pancreas. Three hundred cubic centimeters of peritoneal fluid were present; peritoneal fluid amylase was 14,400 u./100 ml, and protein, 6.8 gm./100 ml. Cholecystectomy and cystogastrostomy were performed. Postoperatively the patient did well; serum and urinary amylase returned to normal.

*Comment:*—A case of pancreatic ascites associated with pancreatic pseudocyst which responded to internal drainage.

*Case 3:*—B. M. G., a 50-year old white man with a long history of alcoholism, developed abdominal pain, nausea and vomiting two days before admission. He also developed gangrene of the toes of left foot. He had marked epigastric tenderness. Serum amylase was 292 units; urinary amylase was 870 u./hr. Hgb., 14.4; Hct., 41.5; WBC, 19,000; polys, 85; stabs, 3 and lymphocytes, 14. Prothrombin time was normal. SGOT, 58; SGPT, 14. Alkaline phosphatase, 10.7; total bilirubin, 0.7; total protein, 6.2; albumin, 2.0, BUN, 20; calcium, 7.5. On laparotomy gallstones were found in the common duct. Liver was normal. There were dense adhesions in the tail of the pancreas and pancreas was swollen and boggy. Eight hundred cubic centimeters of seropurulent ascitic fluid were present. Ascitic fluid amylase was 12,500 units; lipase was 13.6; protein was 5.6; cell count was 19,800. Ascitic fluid culture was negative at 48 hours. A left femoral embolectomy was also performed.

*Comment:*—In this case pancreatic ascites occurred in association with acute pancreatitis without pseudocyst.

*Case 4:*—K. B., a 48-year old white man was involved in an auto accident one week before admission. He suffered mild blunt trauma to the abdomen. He developed abdominal pain, nausea and vomiting 48 hours before admission. The abdominal pain radiated to the back and abdomen became rigid and tender. He developed ascites. Abdominal film showed ascites and many distended loops of small bowel. Upper gastrointestinal series showed anterior displacement of the stomach and widening of the duodenal loop. Hgb., 22.0; Hct., 63.6; WBC, 18,900; polyps, 83; lymphocytes, 15. After hydration, Hgb. was 14.9; Hct., 44.1, WBC 11,500. Serum sodium, 153; phosphorus, 5.5; BUN, 27; creatinine, 2.0; serum amylase, 1,170; urinary amylase, 2,210 u./hr. $Ca^{++}$, 6.8; total protein, 6.5; albumin, 3.0. SGOT was 250; alkaline phosphatase, 100; total bilirubin, 3.8; direct, 2.5 Blood sugar was 335; serum acetone was negative. Serum lactate 49.6 (normal 3-12 mg.%). Prothrombin time was normal. Ascitic fluid, no bacteria on smear and culture was negative at 48 hours. Specific gravity of ascitic fluid, 1,022; RBC, 50,000/cu. mm. and WBC, 38,400/cu. mm. with 88 polyps and 12 lymphyocytes and protein was 4.2. Ascitic fluid amylase was 11,820 Somogyi units. Arterial blood gases showed a pH of 7.37; $pO_2$, 74.5 and $pCO_2$, 21.3. The patient continued to deteriorate and expired. On autopsy, there was extensive diffuse hemorrhagic pancreatitis with a hematoma in the head of the pancreas; there was hemorrhagic peritoneal fluid. There was no pseudocyst and no pancreatic ductal rupture.

*Comment:*—This is a case of hemorrhagic pancreatic ascites associated with hemorrhagic pancreatitis without pseudocyst or pancreatic ductal rupture.

*Case 5:*—J. T. H., a 55-year old white man was hospitalized with a one-week history of weakness and bilateral dull upper abdominal pain of four days' duration. He had a renal transplant performed two years before admission and was on immunosuppressive therapy. He had upper abdominal tenderness. Serum amylase on admission was 1,000 Somogyi units. Later on the day of admission, he developed abdominal distention, marked abdominal pain and guarding. Hgb. was 6.3 and Hct., 19.9. Other laboratory data were: WBC, 9,600; BUN, 114; creatinine, 5.6; Na, 142; K, 6.3; Cl, 106; $CO_2$ 11; total protein, 5.8; albumin, 2.9; SGOT, 150; total bilirubin, 4.1; direct, 3.4; $Ca^{++}$, 10.4; $pO_4$, 4.4 The patient developed upper gastrointestinal bleeding but was considered to be too sick for fiberoptic endoscopy. Blood transfusions were given. Platelet count was 98,879/cu. mm.; platelet adhesiveness, 28% (normal 40 ± 9%), platelet aggregation was impaired. At the time of operation he was found to have hemorrhagic pancreatitis with serosanguinous peritoneal fluid which had amylase of 1,788 Somogyi u./100 ml. and protein of 5.1%. After the operation he developed sepsis and become anuric. Renal blood flow study with $^{99m}$Tc pertechtinate showed nonvisualization of the transplanted kidney. He also developed pneumonia and left pleural effusion. Renal biopsy of the transplanted kidney showed cortical necrosis. Peritoneal dialysis was carried out. The patient's general condition continued to deteriorate; he became obtunded and expired three weeks after admission. On autopsy, rejected kidney transplant showed cortical necrosis and there was bilateral end-stage renal disease, mild fatty liver, acute erosive gastritis and acute hemorrhagic pancreatitis with extensive fat necrosis. There was no pseudocyst.

*Comment:*—This is a case of acute pancreatitis due to prednisone or imuran. Hemorrhagic pancreatic ascites occurred due to hemorrhagic pancreatitis.

*Case 6:*—R. S., a 59-year old black man with a history of heavy drinking for two weeks before admission, developed nausea and vomiting four days before admission. On examination he was found to be in obvious distress and was confused and jaundiced. Abdominal examination showed tenderness in the epigastrium and presence of ascites. Hgb., 10.5; Hct., 32.0; SGOT, 2,000; SGPT, 657; Ca, 8.8; BUN, 23; creatinine, 3.4. Serum amylase, 302 Somogyi units; WBC, 5,300/cu. mm.; prothrombin time was 36.0 sec.; Na, 138; K, 4.0; Cl, 86; $CO_2$ 27; total bilirubin, 7.5; direct, 5.6; alkaline phosphatase, 6.6; total protein, 5.4; albumin, 2.1. Urinary amylase was 800 u./hr. Plain film of the abdomen showed ascites. Ascitic fluid showed a cell count of 1,130/cu. mm. with 20 polyps and 76 lymphocytes; protein, 1.4 gm./100 ml. and amylase, 1,279 u./100 ml. ECG showed poor R wave progression and increased QT interval. Arterial blood gases showed a pH of 7.10; $pO_2$, 137 and $pCO_2$, 34.0. The patient developed more abdominal distention, continued to deteriorate, became hypotensive and anuric and expired 24 hours after admission. On autopsy he was found to have acute hemorrhagic pancreatitis with fat necrosis of the mesentery, acute erosive gastritis, severe fatty liver and pulmonary edema.

*Comment:*—In this case, ascites might have been due to portal hypertension secondary to acute fatty liver but a high amylase content of the ascitic fluid favors pancreatic origin.

*Case 7:*—H. R. S., a 47-year old white man developed jaundice one week before admission. Along with jaundice he also developed upper abdominal pain and generalized pruritus. He had long history of alcohol abuse. On examination he had scleral icterus and mild hepatomegaly. There were no physical stigmas of cirrhosis. Hgb., 13.2; Hct., 41; total protein, 6.8; albumin, 3.3; SGOT, 273; alkaline phosphatase, 34.0; total bilirubin, 26; direct bilirubin, 25.2; SGPT, 198. An upper gastrointestinal series showed indentation in the postbulbar area. Serum amylase was 100 Somogyi units; urinary amylase was 1,100 Somogyi u./hr. A radioactive Rose bengal liver scan showed complete biliary obstruction. At operation, he was found to have pancreatitis and had localized collection of serosanguinous fluid in the head of the pancreas obstructing the common bile duct. The abscess was not continuous with the pancreatic ductal system. Three hundred fifty cubic centimeters of serosanguinous peritoneal fluid were present. Ascitic fluid culture showed no growth; cell count was 19,700 with 90% polymorphs; protein, 2.75 gm.% and amylase, 67,774 Somogyi u./100 ml. The patient underwent exploration of the common duct, choledochoduodenostomy and drainge of the pancreatic abscess. Needle biopsy of the liver showed changes compatible with extrahepatic obstruction. Postoperative course of the patient was unremarkable.

*Comment:*—This patient had pancreatic ascites in association with pancreatic abscess which was secondary to alcoholic pancreatitis.

*Case 8:*—W. A. L., a 56-year old white man presented with periumbilical abdominal pain of one day's duration. He had a long history of chronic seizure disorder. He denied any alcohol intake. On examination he was found to be acutely ill with a temperature of 39° C. Abdomen was diffusely tender and shifting dullness was present. Hgb. was 14.5; Hct., 44.5; WBC, 13,200. Serum amylase was 1,330 Somogyi units, urinary amylase, 8,000 Somogyi u./hr. Serum calcium, 8.7; Na, 134; K, 4.2; Cl, 105; $CO_2$, 25. Chest x-ray and liver tests were normal. On abdominal exploration there was acute edematous pancreatitis and pancreatic fat necrosis. Peritoneal fluid was serous with a total cell count of 80/cu. mm.; amylase, 1,361 Somogyi u./100 ml.; protein, 4.3 gm./100 ml.; there was no bacterial growth at 48 hours. Postoperatively the patient's serum and urinary amylase gradually returned to normal and he became asymptomatic.

*Comment:*—The etiology of pancreatitis on this patient is not known. It may be secondary to unrecognized mild abdominal trauma as a result of seizure disorder.

## COMMENT

It seems that in cases of pancreatitis, there is retroperitoneal obstruction of pancreatic lymphatics[15] which may result in massive pancreatic ascites. This concept is supported by experimental and lymphangiographic studies.[53-55] The clinical picture includes an episode of acute pancreatitis which does not subside and there is persistence of fever, leucocytosis, hyperamylasemia, development of ascites and clinical deterioration. Sometimes it can present as unexplained ascites and determination of serum, urinary and ascitic fluid amylase and lipase is helpful in diagnosis.[2, 7, 9] In these cases, there is a high incidence of pancreatic pseudocysts, hemorrhagic pancreatitis and internal pancreatic fistula. In the present series, two cases were associated with pseudocysts, three were associated with hemorrhagic pancreatitis and three were associated with acute edematous pancreatitis. Pseudocyst and pancreatic ductal rupture can be diagnosed by endoscopic or operative pancreatogram. Pseudocysts can also be located by abdominal ultrasonography and abdominal computerized axial tomography.

High enzyme and protein concentration in the ascitic fluid are characteristic of pancreatic ascites. Pancreatic ascites is a distinct clinical entity which should be differentiated from cirrhotic, tuberculous or malignant ascites. Occurrence of pancreatic ascites seems to be a serious event; four of these eight (50%) patients died.

The correct therapy for all patients with pancreatic ascites has not been established.[31] It seems that in cases of traumatic pancreatitis associated with pseudocyst or pancreatic ductal leak, early surgical treatment consisting of partial pancreatectomy or internal drainage of the pseudocyst or ruptured pancreatic duct should be carried out. In cases of alcoholic pancreatitis complicated by pancreatic ascites, it is reasonable to carry out medical treatment if the patient's condition is stable because spontaneous resolution of pancreatic ascites can occur.[5] One patient in the present study showed spontaneous resolution. Parenteral hyperalimentation and elemental diet[5, 56, 57] may be useful in the treatment of pancreatic ascites. If the ascites does not improve or patient's condition worsens, then abdominal exploration becomes necessary. Radiation inhibits pancreatic secretion and three cases of pancreatic ascites have been successfully treated by low dose radiotherapy,[27, 36, 41] however, value of this mode of therapy remains to be proven.[58, 59]

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# Acute Cholecystitis Secondary to Unusual Gallstones

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Gallstone formation around metallic foreign bodies is an unusual cause of acute cholecystitis. Two cases of penetrating abdominal trauma are described in which metallic fragments served as the nidus for calculus formation and later precipitated an acute abdominal problem.

Foreign bodies in the gallbladder are rarely the cause of gallstones. On occasion, however, parasites, pins, bones, sutures and food material have served as the nidus for such calculi.[1] Penetrating abdominal trauma with lodgement of metallic fragments in the gallbladder resulting in stone formation is even more uncommon.[2] The purpose of this report is to describe two patients with gunshot and shrapnel wounds of the abdomen. Both developed cholelithiasis around the retained fragments and presented with acute cholecystitis several years following injury.

## CASE REPORTS

*Case 1:*—A 22-year old man was admitted to the Phoenix Veterans Administion Hospital because of fever, nausea, vomiting and right upper quadrant pain. Sixteen months previously, during an altercation, he had been shot in the abdomen. The main entry of the shotgun blast was in the left upper quadrant but numerous pellets lodged over the entire abdomen. Corrective surgery included closure of numerous perforating wounds of the small intestine and a partial resection of the transverse colon. After a long, stormy, postoperative course, complicated by intra-abdominal infection and upper gastrointestinal hemorrhage, he was discharged. On the current admission, he was an obese white man with a temperature of 38° C. He was not jaundiced. His gallbladder was palpably enlarged and tender. The serum bilirubin, alkaline phosphatase, and SGOT were normal. The white blood count was 15,800/cu. mm. with a shift to the left. The gallbladder did not visualize on two day oral cholecystogram. Intravenous cholangiography revealed a large gallstone with a single buckshot in its center (Fig. 1). Numerous other buckshot were seen. A cholecystectomy was performed. The gallbladder and cystic duct were surrounded by adhesions. Inside the gallbladder was a single oval calculus measuring 2.8 cm. in diameter. It was quite soft and on cut section a single buckshot was seen (Fig. 2). Analysis of the stone was positive for bilirubin and cholesterol. The patient made an uneventful recovery.

*Case 2:*—A 28-year old man was admitted for evaluation of severe right upper quadrant pain which required narcotic injection for relief. Four years before, he had

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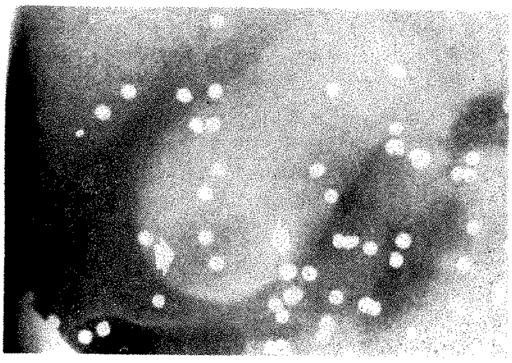

Fig. 1—Intravenous cholangiogram with numerous buckshot present in the area of the gallbladder. Arrows outline a large gallstone.

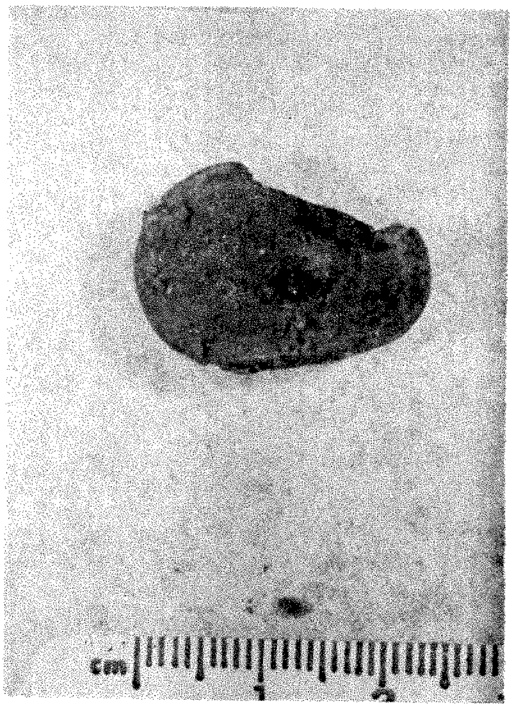

Fig. 2—Cross section of calculus with pellet in its center.

sustained a shrapnel wound in the right upper quadrant while serving in Vietnam. An exploratory laparotomy was done at that time. Lacerations of the stomach and liver were repaired. He remained well until two years before the present admission when he noted intermittent right upper quadrant pain which was accentuated on bending over. On the present admission, the physical examination revealed a well nourished white man with marked right upper quadrant tenderness and multiple abdominal scars. He was neither jaundiced nor febrile. Alkaline phosphatase, bilirubin and SGOT were normal. An upper gastrointestinal series showed a metallic fragment in the right upper quadrant near the duodenal bulb (Fig. 3). Fluoroscopy during the gallbladder series demonstrated the fragment moving freely within the gallbladder which showed fair concentration of the contrast material. A cholecystectomy was done. The gallbladder was surrounded by dense adhesions and contained a solitary stone measuring 1.5 cm. in diameter. Inside the stone was the shrapnel fragment seen on x-ray. The residual stone analysis showed bilirubin and cholesterol.

## COMMENT

The two patients described are noteworthy because they demonstrate that penetrating abdominal injuries with deposition of foreign material in the gallbladder can lead to the formation of gallstones and acute cholecystitis. Foreign bodies of the biliary tree acting as a nidus for gallstone formation are unusual. Most gallstone centers contain bilirubin pigment, bile salts and proteinaceous material. Operative residuals such as ligatures, tubes and suture material may form concretions which precipitate acute gallbladder symptoms.[3] Nauche in 1878 and Eastman in 1909 first reported cases in which steel needles acted as gallstone nidi.[3, 4] Ingestion of pins and chicken bones may cause acute cholecystitis.[5, 6] Morse reported a large gallstone forming around a piece of copper wire.[1] Toothpicks may also lodge in the gallbladder and cause an acute abdomen.[7] The most common foreign bodies responsible for gallstone formation are the ova of parasites, especially *Ascaris lumbricoides*.[1]

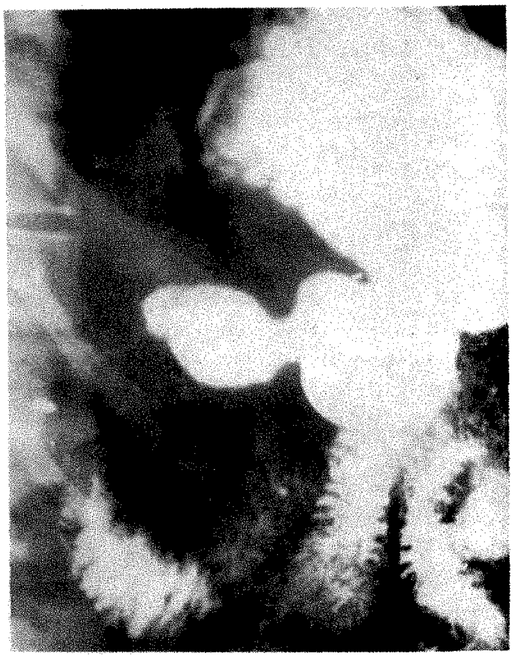

Fig. 3—Upper gastrointestinal series with metallic fragment near duodenal bulb. Fluoroscopy showed it to be in the gallbladder.

In these two patients, the nidi for stone formation were buckshot and a missile fragment. Ban reviewed the literature on foreign bodies in the biliary tree covering a 75-year period and found only two cases of missile fragments causing gallstones.[2] Goldhan retrieved a copper bullet from the cystic duct of a 36-year old man who sustained a bullet wound 14 years previously.[8] Shrapnel and bullets may lodge in the common duct and produce ductal obstruction.[3, 9]

Biliary tract foreign bodies due to penetrating injuries usually have a prolonged interval from initial injury to the appearance of symptoms. In our patients, symptoms developed two and four years after injury. Both presented with signs of acute cholecystitis without any evidence of hepatic dysfunction. In one, changes in position precipitated pain. Here, the piece of shrapnel may have been impinging into the cystic duct. Examination of the stones showed an outside shell of cholesterol and bilirubin, precipitated around foreign body in a ring-like arrangement. This layering indicated gradual growth of the stone. In both cases, the diagnosis of foreign bodies in the gallbladder was suspected clinically and confirmed by fluoroscopy of the gallbladder prior to surgery. The diagnosis should be considered if metallic fragments are seen on abdominal x-rays in a patient with findings of acute cholecystitis.

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# BCG Treatment of Crohn's Disease

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Among 53 patients with documented Crohn's disease, 30% manifested a defect in delayed hypersensitivity demonstrated by negative DNCB skin tests and significant ($p < 0.01$) T-lymphocyte hyporeactivity. A double-blind controlled trial was conducted to evaluate oral Bacillus Calmette-Guerin (BCG) therapy in nine of these patients with Crohn's disease and deficient cellular immunity. All patients had a Crohn's Disease Activity Index (CDAI) greater than 150 (at least moderate activity) upon randomizaion to BCG (five patients) or placebo (four patients) treatment for six to 12 months. No significant differences between BCG and placebo treatment were found in the CDAI, laboratory tests and gastrointestinal roentgenograms. We conclude that the disturbance in cell-mediated immunity in patients with Crohn's disease probably is a manifestation of the disease rather than an etiological factor and that immunostimulation with oral BCG is not effective therapy.

## INTRODUCTION

Recently, immunological investigations of Crohn's disease have provoked interest in the relationship of immune-mediated phenomena to the pathogenesis of this disease.[1, 2] Attention thereby has been drawn to the depressed T-lymphocyte activity and cellular responsiveness found in some patients with Crohn's disease[3] and the possibility that this decreased responsiveness might causally be related to pathogenesis or perpetuation of the disease. As a therapeutic application of this concept, in an analagous situation, Bacillus Calmette-Guerin (BCG) immunostimulation has been utilized in patients with malignancy.[4] Furthermore, a salutory effect of BCG treat-

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ment in Crohn's disease has been reported in an uncontrolled study.[5] Accordingly, our aim was to determine in a controlled study the effect of oral BCG immunostimulation therapy in patients with Crohn's disease and deficient cellular immunity.

## SUBJECTS AND EXPERIMENTAL DESIGN

The diagnosis and extent of Crohn's disease were determined by history, physical examination, proctosigmoidoscopy, barium roentgenograms of the small and large intestine and histologic specimens obtained by rectal biopsy or at operation. Patients who had received steroid or immunosuppressive therapy during the prior three months were not eligible.

Disease activity was determined by application of the Crohn's Disease Activity Index (CDAI) formulated by the National Cooperative Crohn's Disease Study.[6] The CDAI is calculated from data on loose stools, abdominal pain, general well-being, extraintestinal manifestations, medications, abdominal mass, hematocrit and body weight. A CDAI of at least 150 (moderate activity) was required for entry. Cellular immunity was determined *in vivo* by application of 2,4 dinitrol-1-chlorobenzene (DNCB) skin tests and *in vitro* by estimation of T-lymphocyte reactivities to several dilutions of phytohemagglutinin (PHA) and concanavalin A (con A). Of 53 patients with Crohn's disease, 18 (30%) manifested a defect in cellular immunity (negative DNCB skin test) and nine of these gave informed consent to participate in this double-blind, randomized, controlled trial.

The nine DNCB-negative Crohn's disease patients (six women and three men) had an age range of 17-68 years with an average of 42 ± 5.3 SEM. The duration of the disease since the initial diagnosis ranged from one to 26 years, with an average of 12.3 ± 2.7. Four of the patients had involvement only of small bowel, four both small and large bowel, and one only large bowel. All patients had at least moderately active Crohn's disease, with an average CDAI of 264 ± 26.

Five patients (three women and two men) were randomized to receive oral BCG vaccine, two vials weekly for 12 weeks, then every other week for 12 weeks, and finally monthly up to six months. Four patients (three women and one man) were randomized to receive placebo according to the same regimen. The mean age of patients, duration of disease and CDAI did not differ significantly between the BCG and placebo groups at randomization. Three patients in the BCG treatment group and two in the placebo group were taking Azulfidine at the time of randomization and continued this during the trial.

The Tice strain of BCG vaccine produced by Chicago Research Foundation contained 4 × $10^8$ to 6 × $10^8$ viable organisms per vial in a lyophilized form (net weight 16 mg. per vial). The vaccine remains stable for six months when frozen. Immediately prior to administration, two vials of BCG were thawed, mixed with four ounces of grape juice and ingested by the patient. Those patients receiving placebo ingested grape juice alone in the same manner. The preparation of the vaccine or placebo was not seen by the patient or physician.

## OBSERVATIONS

Clinical history, physical examination, CBC, urinalysis, serum alkaline phosphatase, bilirubin and SGOT were done initially, at one and three months and every three months after initiation of therapy.

Serum lysozyme, protein electrophoresis, quantitative immunoglobulins, chest

TABLE I

T-LYMPHOCYTE REACTIVITY TO MITOGENS

| Mitogens | Control subjects (N = 15) | Crohn's disease patients | |
|---|---|---|---|
| | | DNCB-positive (N = 10) | DNCB-negative (N = 10) |
| PHA (1:4) | 43,678 ± 3,109 | 46,990 ± 2,269 | 4,234 ± |
| Con A (1:256) | 14,263 ± 1,768 | 12,962 ± 1,893 | 4,733 ± 770 |

Responses to PHA and con A are expressed as counts per minute ± SEM of $^3$H-thymidine uptake by lymphocytes. The dilutions of PHA or con A are indicated in parentheses. The patients with DNCB-negative skin tests manifested significantly lower counts per minute than the DNCB-positive patients or normal controls with PHA ($p < 0.05$) and with con A ($p < 0.001$).

x-ray, upper gastrointestinal, small bowel and barium enema roentgenograms were done initially and at six months and one year. The roentgenograms were evaluated with their sequence and the patients' treatment unknown. The CDAI was determined initially and at 1, 3, 6, 9 and 12 months, based on two consecutive weekly diary records and an examination of the patients.

## DNCB SKIN TESTS

A circular area of skin 2 cm. in diameter on the volar surface of the forearm was surrounded by a plastic disk; 0.1 ml. of a 10% solution containing 100 μg. of DNCB in acetone was applied to the area and evaporated in a stream of air for three minutes. DNCB sensitization, and *in vivo* assessment of T-lymphocyte function, was tested three weeks later by the application to the opposite forearm of 0.1 ml. of a 1% solution containing 10 μg. of DNCB. Skin-test results were interpreted 48 hours later. An area of erythema and induration involving more than 50% of the test site was considered a positive (normal) cell-mediated immune response. Utilizing this method, each of 15 healthy adult volunteers and 26 patients with chronic ulcerative colitis had positive DNCB skin tests.

The DNCB skin test was performed initially in all 53 patients with Crohn's disease and repeated after therapy in the nine DNCB-negative patients participating in the trial. Positive DNCB skin sensitization was found in 37 (70%) of the 53 Crohn's disease patients studied. The DNCB-positive patients appeared to have less extensive radiographically demonstrated Crohn's disease than did the 18 DNCB-negative patients but no significant differences were noted in the CDAI, duration of the disease, or the age and sex of the patients.

## T-LYMPHOCYTE RESPONSE TO T-CELL MITOGENS

*In vitro* T-lymphocyte reactivities to three dilutions of phytohemagglutinin (PHA-M; 2.5 mg./ml.; Difco Laboratories, Detroit, MI) and two dilutions of concanavalin A (con A; 16 mg./ml.; Calbiochem, Los Angeles, CA) were determined in 10 DNCB-positive and 10 DNCB-negative Crohn's disease patients by routine methods.[7] $^3$H-thymidine uptake of replicating lymphocytes was measured by scintillation spectrophotometry and expressed in counts per minute + SEM. T-lymphocyte responses were determined without knowledge of the DNCB skin test.

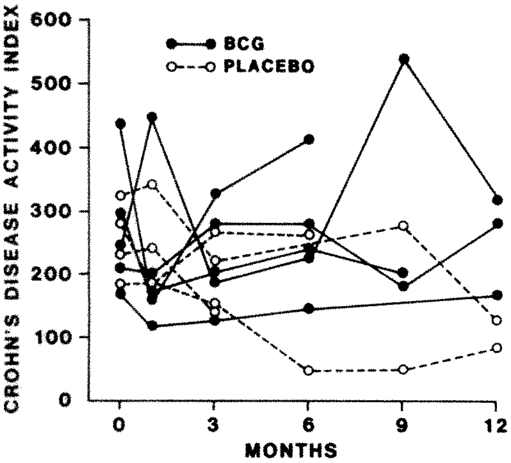

Fig. 1—Crohn's Disease Activity Index (CDAI) during treatment. The CDAI fluctuated in individual patients and demonstrated no BCG or placebo group trends. Three patients (one receiving BCG and two receiving placebo) experienced a remission (CDAI $< 150$) at at least one visit during the trial.

Incubated T-lymphocytes at each of the three PHA dilutions (1/4, 1/16 and 1/64) in the DNCB-positive Crohn's disease patients demonstrated significantly ($p < 0.05$) greater $^3$H-thymidine uptake than in the DNCB-negative group. Peak responsiveness occurred at a PHA dilution of 1/4 (Table I). No significant differences in T-lymphocyte reactivity were noted between the DNCB-positive patients and healthy volunteers with the PHA dilutions of 1/4 and 1/64. At a PHA dilution of 1/16, however, the DNCB-positive patients did exhibit significantly ($p < 0.05$) greater responsiveness than normal controls.

At both dilutions (1/64 and 1/256) of con A the DNCB-positive Crohn's disease patients and the healthy controls manifested significantly ($p < 0.05$) greater $^3$H-thymidine uptakes than the DNCB-negative Crohn's disease patients and this difference was particularly striking at the 1/256 dilution (Table I).

Eight patients with chronic ulcerative colitis (all having positive DNCB skin tests) demonstrated lymphocyte responses to the T-cell mitogens which were not different from those of the normal controls.

## TREATMENT RESULTS

Four patients were followed for 12 months, two for 9 months, and two for six months; one patient withdrew after three months because prednisone was required for arthritis. Although there were fluctuations in the CDAI during treatment, no significant clinical or roentgenographic improvement was found in patients treated with BCG (Fig. 1). The serum lysozome did not correlate with the CDAI. No consistent trends were observed in the results of the laboratory tests of individual patients during the trial. Gastrointestinal roentgenograms also did not change except in one patient receiving placebo in whom the films were interpreted as showing progression of the disease.

No complications of BCG therapy were observed. The DNCB skin tests converted to positive in all five patients treated with BCG but also became positive in one of the four patients treated with placebo.

## COMMENT

BCG stimulates T-lymphocytes, an action which provides the rationale for BCG immunotherapy of cancer, melanoma and leukemia.[4, 8] If defective delayed hypersensitivity were perpetuating the pathology of Crohn's disease, then BCG might be expected to reverse the process.

In 1970 Geffroy reported successful results from BCG immunotherapy in an uncontrolled study of Crohn's disease.[5, 9, 10] Weekly BCG scarification in nine patients was followed by improved appetite, decrease diarrhea and weight gain; four of six patients showed roentgenographic improvement.[9] We have not confirmed Geffroy's results. Our study differed from that of Geffroy in that we used oral BCG in a double-blind, controlled manner in an immunodeficient subpopulation of patients with Crohn's disease. Moreover, our use of the CDAI may provide a more accurate assessment of the clinical course. Oral BCG places the stimulus closer than parenteral BCG to the intestinal pathology and in our study induced DNCB skin test reactivity but conceivably may not have been as effective immunostimulation as BCG administered by scarification. Oral BCG vaccine for prevention of tuberculosis, however, has had widespread successful application.[11] Furthermore, in a more recent report from France, Dupuy and colleagues[12] also did not find BCG administered by scarification efficacious in Crohn's disease.

Neutrophil dysfunction has been demonstrated in Crohn's disease.[13] Levamisole, an agent that stimulates motility and function of neutrophils[14] has been reported to be effective in maintaining remission in patients with Crohn's disease.[15] This study, however, was uncontrolled and levamisole may either augment or suppress the immune response.[16]

The significance of a disturbance in cell-mediated immunity in 30% of the patients with Crohn's disease in contrast to the positive DNCB skin tests and normal lymphocyte response to T-cell mitogens in all of the patients with chronic ulcerative colitis is unknown. The literature contains conflicting conclusions regarding the integrity of cell-mediated immunity in Crohn's disease.[1, 17] possibly explained by the effects on T-lymphocyte function of disease activity, steroid or immunosuppressive medications, or different methodologies. Nevertheless, the lack of clinical response to BCG immunostimulation among our immunodeficient patients with Crohn's disease is compatible with the concept that their depressed T-cell function is a manifestation rather than a cause of the disease.

## ACKNOWLEDGMENT

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# Pernicious Anemia Caused by Crohn's Disease of the Stomach

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A patient with granulomatous gastritis is described. Two years after the presentation of his gastric disease he developed pernicious anemia. Lack of intrinsic factor production secondary to Crohn's disease of the stomach is felt to be the cause of his Vitamin $B_{12}$ malabsorption.

Megaloblastic anemia has been noted often in patients with Crohn's ileitis and is secondary to loss of Vitamin $B_{12}$—intrinsic factor binding sites in the terminal ileum. This report presents an unusual case of pernicious anemia resulting from a lack of intrinsic factor production secondary to Crohn's disease of the stomach.

## Case Report

A 32-year old black man presented at the Nashville General Hospital in January, 1974 with several years of abdominal pain and recent symptoms of gastric outlet obstruction. Hematology survey showed his hematocrit to be 46% with white blood cell count, 4,100. Upper gastrointestinal series showed obstruction of the antrum and a deformed duodenal bulb and gastroscopy confirmed a stenotic distal antrum. Gastric analysis with maximum Histalog stimulation demonstrated achlorhydria. At operation splenomegaly and mesenteric lymphatic hypertrophy were noted as well as a normal duodenum and small bowel. At gastrotomy a thickened stenotic antral mucosa was seen without ulceration. A posterior gastrojejunostomy was performed. Biopsies of the gastric mucosa revealed granulomatous inflammation with multinucleated giant cells and the same changes were found in periaortic and celiac nodes (Fig. 1).

The patient did moderately well but continued to be bothered by abdominal discomfort and a sore mouth and was admitted to St. Thomas Hospital November, 1975. The upper gastrointestinal series (Fig. 2) showed that the distal antrum was constricted with an obstructed pylorus and the gastroenterostomy patent. Gastroscopy demonstrated friable inflamed gastric mucosa without frank ulceration; the distal antrum was stenotic and the gastroenterostomy anastomosis normal. Hematology survey showed hematocrit, 31%; reticulocytes, 1.2%; white blood cell count, 3,400; mean corpuscular (red cell) volume, 79 and a bone marrow section showed absence of iron with no other abnormalities. Acid fast cultures of bone marrow were negative. Stools for blood (occult) were negative × 3. Serum gastrin was less than 100 pg./ml. He was treated with iron and low doses of Azulfidine and prednisone.

In April, 1976 he was readmitted because of malaise, weight loss and particularly because of loss of taste and a painful

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From the Department of Gastroenterology, Department of Medicine, St. Thomas Hospital and The Department of Gastroenterology, Vanderbilt University Medical School.

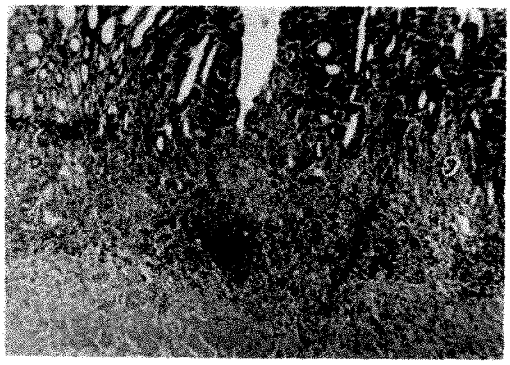

Fig. 1—Surgical biopsy of gastric mucosa revealing granuloma and diffuse infiltration of mucosa by inflammatory cells (Hematoxylin and eosin, original magnification x40).

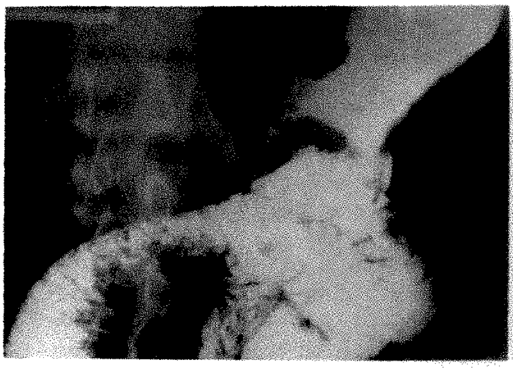

Fig. 2—Upper gastrointestinal series showing constriction of distal antrum and patent gastrojejunostomy.

mouth and tongue. Neurologic examination was normal. Hematologic evaluation revealed hematocrit 24% with the following indices: MCV, 84; MCH, 26; MCHC, 30. His white blood cell count was 1,900 with occasional hypersegmented neutrophils and the red cells demonstrated marked anisocytosis, poikilocytosis and hypochromasia. Bone marrow sections contained noncaseating granulomas and showed marked hypercellularity due to proliferation of megaloblasts; minimal (1+) iron was noted. Serum tests showed LDH, 3,600 with the major portion in fractions LDH-1 and LDH-2; folic acid, 2.5 (normals 5-20) and $B_{12}$, 230 (normals 300-900). A small bowel series was normal. Gastric analysis confirmed achlorhydria after a maximum Histalog dose. Schilling test demonstrated 1.5% excretion of marker in 24 hours and increased to 24.7% excretion with hog intrinsic factor. Histoplasmosis serology was negative.

The patient had a dramatic response to parenteral Vitamin $B_{12}$ with immediate loss of malaise and all oral symptoms and a rise in reticulocytes (0.7-8.0% in three days) and hematocrit. The improvement was definitely felt to be due to Vitamin $B_{12}$ and not to folate replacement, as folic acid was not given until after the Schilling test and the patient did not eat well until his oral symptoms improved after parenteral Vitamin $B_{12}$. His only drugs are parenteral Vitamin $B_{12}$ and oral folic acid. In June, 1976 follow-up gastroscopy revealed nodular stenotic inflammation of the distal stomach with normal appearing mucosa proximally. Multiple gastric biopsies revealed inflammation with round cell infiltration involving both the proximal and distal stomach (Fig. 3). No granulomas were seen in the biopsies. Parietal cell and intrinsic factor antibodies were not present in the serum.

## COMMENT

Crohn's disease involving only the stomach is rare.[1-3] A 1972 literature review reported only 12 cases[3] and in 14 patients with gastroduodenal Crohn's disease seen over 10 years at the Cleveland Clinic none had disease limited to the stomach.[2] The radiologic appearance of gastric Crohn's disease is one of antral narrowing and sparing of the upper stomach. Often the antrum, pylorus and duodenal bulb are blended into a single tubular structure, which has been dubbed the "pseudo post-Billroth I" appearance.[4] In a radiologic study of six cases of gastric Crohn's disease the abnormalities were confined to the antrum with contigu-

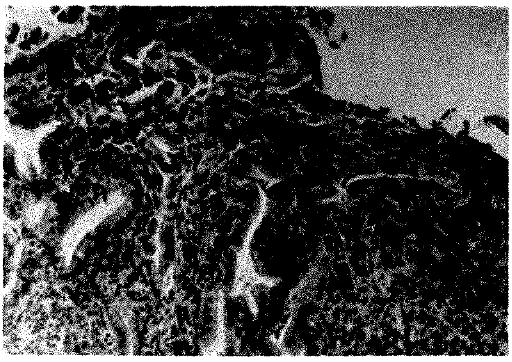

Fig. 3—Endoscopic biopsy of gastric body showing diffuse infiltration by mononuclear cells and decrease in number of parietal cells (Hematoxylin and eosin, original magnification x40).

ous involvement in the duodenum in every case.[5] These cases often demonstrate mucosal nodularity, limited distensibility, thickened folds, and occasionally shallow ulcers.

Fahami, et al[6] have classified granulomatous gastritis into three groups: 1. associated with Crohn's disease; 2. associated with sarcoidosis and 3. primary granulomatous gastritis. Primary granulomatous gastritis affects older patients, usually between 60 and 80 years of age. Gastric sarcoidosis is often associated with insignificant involvement of the stomach and the extraintestinal sites are usually apparent.[7] Some of the older published cases of gastric sarcoidosis may have actually been Crohn's gastritis.[7] Crohn's disease is a nonspecific inflammatory process for which there is no specific test and the diagnosis rests on a combination of clinical features and typical (but not pathognomonic) morphologic changes. The present cases is clinically similar to other published cases of Crohn's gastritis, although if bowel involvement had been present the diagnosis would be even more secure. Nevertheless, Crohn's gastritis best describes this patient's disease.

Endoscopically Crohn's disease might be suspected from mucosal nodularity, thickened folds, antral narrowing and aphthous ulcers but there are no pathognomonic features.[2] Endoscopic biopsies revealed granulomatous inflammation in only two patients of 9 in the Cleveland Clinic series[2] and these two biopsies came from the base of ulcers. These biopsies most generally show chronic inflammation without granuloma, as in this patient.

Gastric secretory data is almost nonexistent in the reported cases of gastric Crohn's disease. A 17-year old boy who was reported in 1972 had basal acid output of less than 0.5 mEq./hr. with 11 mEq./30 min. after Histalog stimulation.[3] The achlorhydria of our patient could result from granulomatous or nonspecific inflammatory involvement of the fundus and body or from severe gastric atrophy. The gastric biopsies of the body and fundus showed an active inflammation and thus infiltration of the mucosa by Crohn's disease rather than atrophy seems most likely. Since the parietal cells produce both HCl and intrinsic factor, the development of pernicious anemia and achlorhydria must reflect a destruction or replacement of parietal cells. His serum gastrin was under a 100 pg./ml. when studied on two occasions in April, 1976 and a continued low serum gastrin would remove a trophic factor to the parietal cells and be one additional factor in the lack of parietal cell function.

The existence of bone marrow granuloma is also a rare manifestation of Crohn's disease and has been recently reported.[8] The differential diagnosis of granulomatous gastritis with bone marrow involvement should include infectious causes but the negative bone marrow culture for mycobacteria and the negative serology for histoplasmosis excludes the two most likely alternatives to Crohn's disease. Serum folate levels in Vitamin $B_{12}$ deficiency may be low, normal, or high and the low folate level of our patient is consistent with Vitamin $B_{12}$ deficiency alone. The interrelationships between Vitamin $B_{12}$ and folate in pernicious anemia are not fully understood.[9] Also poor folate intake or some other acquired form of folate malabsorption was not excluded.

The diffuse atrophic gastritis seen in classical pernicious anemia is associated with lymphocytic infiltration of the mucosa. The cause of this atrophy is unknown but a popular theory is that it results from immune processes and there is evidence of both delayed hypersensitivity and serum antibodies.[10] Antibodies to parietal cells are found in up to 90% of persons with pernicious anemia but are nonspecific and occur in 62% of patients with atrophic gastritis and in many patients with thyroid disease. Antibodies to intrinsic factor are more specific for pernicious anemia but are only found in approximately 70% of patients.[11] Neither parietal cell nor intrinsic factor antibodies were present in this patient; this suggests that the mechanism of parietal cell dysfunction is different in this case than in classical addisonian pernicious anemia. The loss of parietal cells and the inflammation of the gastric mucosa is likely a direct result of infiltration of the stomach by Crohn's disease rather than a response to an immunologic stimulus.

Clearly this patient had malabsorption of Vitamin $B_{12}$ caused by lack of intrinsic factor. His symptoms, hematologic profile, and low serum $B_{12}$ level establish a deficiency of Vitamin $B_{12}$ and the Schilling test establishes the lack of intrinsic factor. The evidence is like-wise convincing that this intrinsic factor deficiency is caused by Crohn's disease of the stomach because of its classic, albeit rare, radiologic, endoscopic and pathologic presentation and the accompanying achlorhydria.

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***Clinical Vignette***

# Malignant Esophagopulmonary Fistula Complicating Achalasia

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## INTRODUCTION

The diagnosis of esophageal carcinoma complicating achalasia is often delayed because symptoms of the carcinoma, e.g. dysphagia and weight loss are easily attributed to the achalasia by both the patient and physician.[1] Furthermore, whereas fistula to the respiratory tree is a distinctly unusual complication of esophageal carcinoma, we are not aware of a single report of esophageal carcinoma with a malignant fistula to the respiratory tree occurring in a patient with achalasia. This report describes such a patient who presented with pulmonary symptoms and in whom an endoscopic diagnosis of a malignant esophagopulmonary fistula was made.

## CASE REPORT

L. S., a 52-year old white housewife with a long history of asthma was admitted to the pulmonary service of Montefiore Hospital and Medical Center with a ten-day history of malaise, fever and a cough productive of green, nonfoul-smelling sputum. She denied weight loss, change in appetite or chest pain. Her past history was significant for 20 years of nonprogressive dysphagia and although she was unaware of any specific gastroenterologic diagnosis, she treated herself intermittently at home with bouginage.

Physical examination revealed a thin woman in no respiratory distress. Vital signs included a temperature of 38° C; blood pressure of 120/70 mm. Hg.; pulse rate of 100/min. and respiratory rate of 22/min. Examination of the head was unremarkable. The neck was supple and venous pulsations were normal. No adenopathy was present. Cardiac examination revealed a normal $S_1$ and $S_2$ with no murmur or rub. Pulmonary examination revealed no dullness to percussion. Diffuse bilateral inspiratory and expiratory wheezes were heard; there was no egophony or whispered pectoriloquy. Abdominal, rectal and pelvic examination were normal.

Laboratory data included a hematocrit of 37% with normochromic and normocytic indices. Leucocyte count was 8,600 (66 polymorphonuclear cells,, 27 lymphocytes, 5 mononuclear cells and 2 eosinophils). Serum electrolytes, BUN, glucose and urinalysis were normal. Arterial blood gas determination performed while the patient was breathing room air showed a $pO_2$ of 68 mm. Hg. Gram stain of the sputum re-

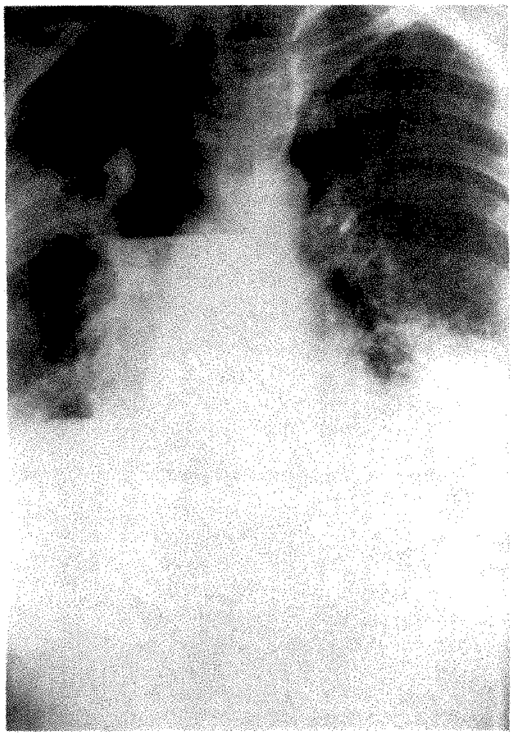

Fig. 1—Chest roentgenogram revealing an air fluid level in the superior segment of the right lower lobe. No gastric air bubble is seen.

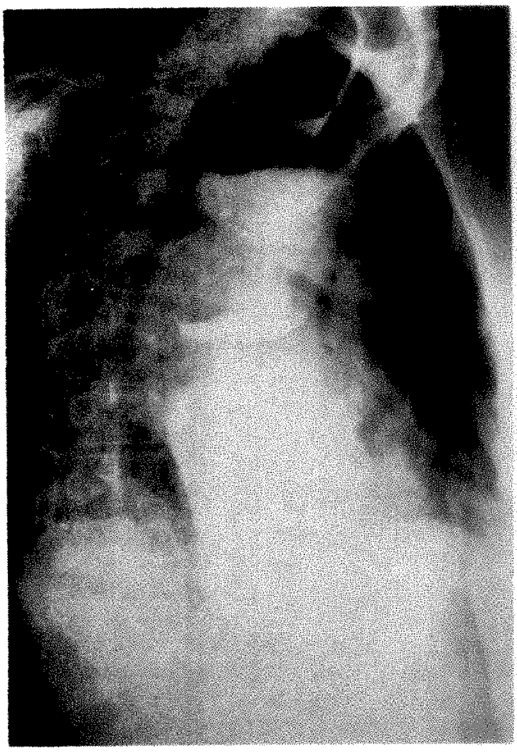

Fig. 2—Barium esophagram revealing a dilated tortuous esophagus with retained food material.

vealed sheets of polymorphonuclear leucocytes with many gram positive and gram negative organisms. A Ziehl-Neelsen stain was negative for acid fast bacilli. Blood cultures were sterile; sputum cultures revealed normal oral flora. A roentgenogram of the chest demonstrated an air fluid level in the superior segment of the right lower lobe. There was no mediastinal widening and no gastric air bubble was seen (Fig. 1).

The patient was treated with 1.2 million units of penicillin intravenously every four hours and postural drainage performed several times daily. The fever and symptoms persisted and gentamycin, 80 mg. every eight hours intramuscularly was added to the therapeutic regimen. The patient gradually improved. One week later, an upper gastrointestinal series was performed which revealed a tortuous dilated esophagus with retained secretions. The esophogastric junction had a smooth "bird beak" configuration consistent with achalasia (Fig. 2).

Attempt at esophageal motility was unsuccessful. Esophagogastroscopy was performed under local tetracaine (Pontocaine®) anesthetic and with sedation by intravenous diazepam (Valium®). A fiberoptic gastroscope (Olympus, Model GIF-D) was passed into the proximal esophagus and a large amount of mucoid material aspirated from a widely dilated esophagus. At 30 cm. from the incisors, a friable, irregular 0.5 cm. opening draining purulent material during the expiratory phase of respiration was seen (Fig. 3). Multiple biopsies were taken from this area. The opening was then cannulated (Olympus Can-

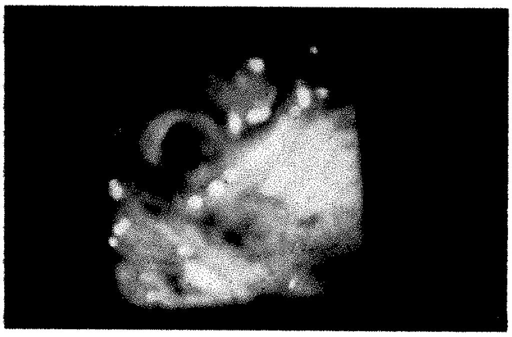

Fig. 3—Endoscopic photograph of the esophago-pulmonary fistula.

nulation Tube #6452) and 5 cc. of diatrizoate meglamine (Hypaque®) injected into the orifice. The contrast material was seen fluoroscopically to fill the bronchial tree of the right lower lobe. Subsequently, the endoscope was passed easily through the narrow distal esophagus which opened as the endoscope approached it. The remainder of the endoscopic examination was normal. Biopsy specimens taken from the proximal draining opening were interpreted as showing squamous cell carcinoma.

The patient was referred to the thoracic surgical service and a two-stage procedure was recommended to resect the esophagus and perform a colonic interposition.

Prior to surgery but under general anesthesia, rigid esophagoscopy was performed. The friable area was again noted at 30 cm. in the dilated esophagus. During the positive pressure phase of assisted ventilation, respiratory secretions and air bubbles were seen to fill the esophagus via this friable area. Surgery was performed by two teams. One team utilized a mid line abdominal incision to mobilize the transverse colon. After securing its vascular pedicle, the colon was transected and anastomosed to the esophagus which had been mobilized through a retrosternal tunnel by the other team. A pyloroplasty was performed and a feeding gastrostomy created. Pathologic sections of the paraesophageal nodes were negative for tumor.

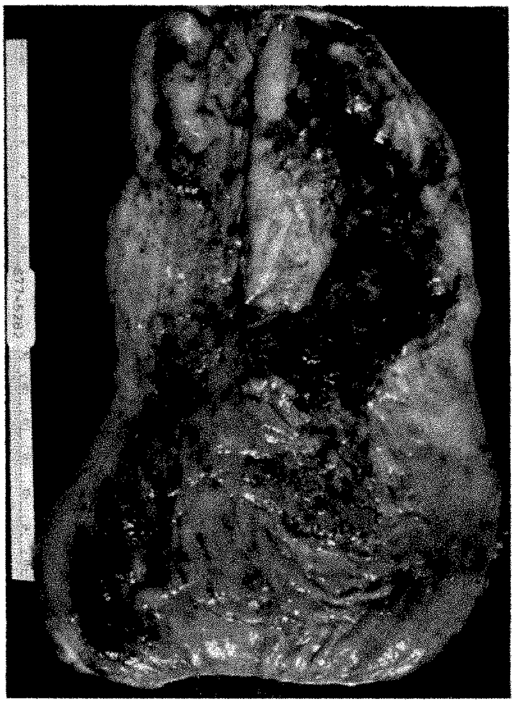

Fig. 4—Gross specimen reveals a dilated esophagus and necrotic carcinoma.

The second stage of the procedure was begun two weeks later. Utilizing a transthoracic approach, the esophagus was mobilized and resected. The fistula was found to communicate with the superior segment of the right lower lobe. The fistula and its communicating pulmonary segments were resected (Fig. 4).

Pathologic examination confirmed the well differentiated squamous cell carcinoma in a dilated esophagus. The pulmonary segments contained metastatic deposits.

Three weeks postoperatively, after patency of the esophagus was confirmed by an esophagram, the patient was discharged. She remains well and asymptomatic six months after surgery.

## COMMENT

Esophageal carcinoma, most often squamous, has been documented to complicate long-standing achalasia in up to 29% of cases.[2] The carcinoma occurs late in the course of the achalasia with an average interval prior to diagnosis of the carcinoma of 17-28 years.[3, 4] With achalasia of such duration, the esophageal dilation that is present delays the usual symptoms caused by mass lesions in the esophagus. Furthermore weight loss and esophageal bleeding are often attributed to the advanced achalasia stasis esophagitis. During this advanced stage, respiratory symptoms occur in approximately one-third of the cases and are usually caused by aspiration of retained esophageal contents.[5] In our case, the respiratory symptoms prompted immediate medical evaluation but led to the diagnosis of esophageal carcinoma with an esophagopulmonary fistula. Respiratory symptoms similarly led to the clinical diagnosis in approximately one-third of the 111 cases of esophagopulmonary fistula collected at Memorial Hospital. Not a single patient in that series was found to have achalasia as the underlying condition.[6]

In addition to the delayed clinical recognition of the neoplasm, the radiologic diagnosis of esophageal carcinoma in achalasia is difficult especially in the "unprepared" esophagus. Thus a regimen of clear liquids for several days and irrigation of the esophagus through a large bore tube is to be recommended. Nonetheless the diagnosis of esophageal carcinoma was missed in 69% of 57 patients with achalasia.[3] Our case thus establishes the value of endoscopy in the evaluation of the patient with achalasia with a change in clinical status and serves to report the unique finding of a malignant esophagobronchial fistula in achalasia.

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The authors are indebted to Drs. A. Buchberg and L. Attai for allowing this report of their patient.

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***Clinical Vignette***

# Fulminant Disseminated Intravascular Coagulation in Advanced Gastric Carcinoma

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A case of fulminant disseminated intravascular coagulation (DIC) in a 51-year old man, presenting with bleeding gastric adenocarcinoma, is reported. In spite of initial hematologic improvement by replacement therapy the patient died on the fifth day after admission. The rare association of DIC with adenocarcinoma of the stomach is discussed.

## CASE REPORT

The patient was a 51-year old male subject who presented to Royal Perth Hospital in July, 1975 with acute hematemesis. He was apparently well until February, 1975 when he developed biliary colic, for which he had cholecystectomy. In February, 1976 he presented with loss of appetite, loss of three stones in weight, increasing shortness of breath and ankle edema. Five weeks before admission he had twice vomited fresh blood. There was no history of aspirin intake or alcoholism.

On physical examination he was found to be pale but not jaundiced. There was minimal ankle edema but the jugular venous pressure was not raised. His pulse rate was 120/min. and regular and the blood pressure was 110/75 mm. Hg. His lungs were clinically clear. Palpation of the abdomen revealed tenderness over the epigastrium and the right hypochondrial region. The liver and spleen were not palpable. Rectal examination revealed melena. There was no lymphadenopathy.

After initial resuscitative measures a panendoscopy was done with the Olympus Fiberendoscope, Model GIF D2, and the findings were as follows: A large growth was seen over the upper part of the lesser curve. This growth had the appearance of a carcinoma of the stomach. There was mild bleeding from the growth surface. Four biopsies were obtained to confirm the malignancy. The duodenum and esophagus were essentially normal. The endoscopic diagnosis of carcinoma of the stomach with bleeding was made. Histological sections of the gastric biopsies confirmed the presence of poorly-differentiated adenocarcinoma of the stomach. The chest x-ray was normal. Other investigations on admission showed the following results: hemoglobin, 79 gm./l.; white blood cell count, 20.7 × $10^9$/l.; platlet count, 162 × $10^9$/l.; erythrocyte sedimentation rate, 6 mm./hr. The blood film showed a moderate degree of anisocytosis and polychromasia, together with a few burr cells. Direct Coomb's test was negative. Prothrombin time, 16 seconds (control 11 seconds). Serum electrolytes and bicarbonate were normal; blood urea 15.4, mmol./l.; serum creatinine, 160 μmol./l.; serum bilirubin, alkaline phosphatase, SCPK and serum calcium were normal; SGOT, 104 u./l.; LDH, 660 u./l.; serum albumin, 21 gm./l. He was transfused with three units of blood and referred for surgery. Since bleeding persisted coagulation studies were performed on the third day after admission with the following results; platelet count, 91 × $10^9$/l.; prothrombin time, 30 seconds (control 11 seconds); thrombin clotting time, greater than 60 seconds (control 10 sec.); activated partial thromboplastin time, 74 seconds (control 38 seconds); fibrinogen titer, 1/9; fibrinogen level, 0.1 gm./l. (normal level, 1.6-3.4 gm./l.); fibrinolysis, normal at two hours; protamine sulfate paracoagulation test, positive. A peripheral blood film showed polychromasia and greater numbers of helmet, burr and fragmented cells, a picture strongly suggestive of microangiopathic hemolytic anemia. These hematological changes were diagnostic of an acute disseminated intravascular coagulation (DIC), together with a probable microangiopathic hemolytic anemia (MHA). He was given a further six units of blood and an attempt was made to treat the DIC with replacement therapy. The administration of cryoprecipitate, fresh frozen plasma, fibrinogen, together with Vitamin K and calcium gluconate, resulted in a return of the thrombin clotting time to normal and a shortening of the abnormal prothrombin time to 18 seconds (control 11 seconds). In spite of this initial hematologic improvement the patient died suddenly on the fifth day after admission. Permission for postmortem was refused.

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## COMMENT

Although microangiopathic hemolytic anemia (MHA) has been not uncommonly reported in patients with adenocarcinoma of the stomach,[1-5] disseminated intravascular coagulation (DIC) has only been rarely associated with gastric adenocarcinoma. In the series of Brain, et al,[5] hematological evidence indicating the probable presence of DIC (in addition to MHA) was found in six out of seven cases of gastric adenocarcinoma. In the series of Al-Mondhiry,[6] DIC was found in eight cases of gastrointestinal tumors (five rectal or colonic carcinoma; one gallbladder carcinoma; one common bile duct carcinoma and one hepatoma) but no case of DIC in gastric carcinoma was reported. The present case is therefore another rare example of DIC secondary to gastric adenocarcinoma.

There are several points of interest, which were absent in previous reported cases.[5] In contrast to marked mucin-production in the gastric adenocarcinomas of the series reported by Brain,, et al,[5] the gastric biopsies of the present case showed only slight mucin production. While all six cases of Brain, et al[5] had definite hematological evidence of MHA, the present case only had suggestive evidence of MHA in the form of "helmet" and "burr" cells, which could possibly have been secondary to the patient's impaired renal function (blood urea 15.4 mmol./l.; serum creatinine, 160 μmol./l.) or gastric hemorrhage. Heparin was not given since there was continuous bleeding from the gastric cancer. It is noteworthy that intravenous administration of normal plasma together with other factors such as fibrinogen and cryoprecipitate was followed by a return to normal of the thrombin clotting time and improvement of the prothrombin time. It is very unlikely that the clotting abnormalities in this patient were secondary to a hemodilution effect of the blood infused since, of the nine units of blood administered six were packed red cells.

It is difficult to explain the sudden death in this patient especially as there was initial improvement in his hematological abnormalities.

The exact mechanism of the intravascular coagulation in patients with carcinoma remains unclear but it has been postulated that the intravascular coagulation is brought about by the entry of thromboplastin originating from the tumor cells in these patients.[5] It has also been postulated that the microangiopathic hemolytic anemia in patients with adenocarcinoma is secondary to intravascular coagulation.[5] An alternative explanation is that the red cell damage and fragmentation may be brought about by direct contact between red blood cells and tumor cells within small blood vessels.[5] This explanation is supported by the findings of tumor emboli in pulmonary arterioles and capillaries in three out of the patients reported by Brain, et al.[5] The validity of this tumor emboli theory may be questioned since tumor emboli may be found in a large number of cancer patients without evidence of microangiopathic hemolytic anemia and conversely, in those carcinoma patients who do have microangiopathic hemolytic anemia, tumor emboli may be absent.

## ACKNOWLEDGMENT

We are grateful to Dr. L. Matz of the Pathology Department, Royal Perth Hospital for reporting on the gastric biopsies.

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***Clinical Vignette***

# Peliosis Hepatis Due to Oxymetholone— A Clinically Benign Disorder

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Peliosis hepatis is a rare hepatic disorder mainly diagnosed at surgery or autopsy. Clinical outcome is thus frequently poor. We report a patient in whom the diagnosis was established by percutaneous needle biopsy. Withdrawal of the steroid medication was followed by a prompt clinical improvement. Although histologic proof of regression is not available, this experience suggests a more favorable prognosis than previously thought possible.

Peliosis hepatis is a rare disorder characterized by the occurrence of blood-filled hepatic spaces. Recent reports[1-4] mainly emphasizing the association with androgenic-anabolic steroid therapy, draw attention to its frequently fatal outcome. Published reports are thus derived largely from autopsy or surgical material. We wish to report a case of peliosis hepatis with a benign clinical course.

## CASE REPORT

M. S., a 67-year old white male had been treated for idiopathic sideroblastic anemia since 1972. Trials of folic acid and pyridoxine were unrewarding and oxymetholone, 200 mg. p.o., q.d. was begun January, 1973. This was continued for 12 months, during which time his hematocrit remained between 29 and 33%. Oxymetholone was discontinued for a 10-week period early in 1974 and his hematocrit subsequently fell to the low 20's. Evaluation April, 1974, for epigastric pain revealed a small pyloric channel ulcer. Oxymetholone (200 mg./day) was reinstituted, along with prednisone (10 mg./day) and he was treated with antacids. He continued on this regimen for the ensuing year. In late May, 1975, he was admitted to New England Medical Center Hospital for management of a left leg cellulitis and renal failure of recent onset. Several episodes of hemoptysis occurred but initial investigations were unrevealing. The cellulitis responded to intravenous oxacillin and open renal biopsy (27 May 1975) under halothane anesthesia demonstrated changes consistent with an allergic type interstitial nephritis. Hydrochlorothiazide, previously instituted for control of peripheral edema, was implicated and therefore discontinued. He was transfused with a total of five units of blood prior to and after the biopsy. Gross jaundice was noted 5 June 1975, five days following discharge from his previous admission.

Past medical history revealed an episode of probable viral hepatitis in 1931.

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From the Department of Medicine, Gastroenterology Service, New England Medical Center Hospital.

TABLE I

LABORATORY DATA

| | 4/74 | 3/75 | 5/12/75 | 6/5/75 | 6/9/75 | 6/23/75 | 7/7 | 8/4 |
|---|---|---|---|---|---|---|---|---|
| SGOT (8-40 U) | 11 | 30 | 37 | 53 | 83 | | 43 | 24 |
| SGPT (8-40 U) | 34 | 59 | 81 | 97 | 155 | 109 | 77 | 31 |
| Alk. Phos. (1-4 Bodansky units) | 1.0 | 1.2 | 2.3 | 2.5 | | | | |
| Bili. (T/D) (mg.%) | 1.3 /0.5 | 2.3 /1.0 | 4.9 /1.8 | 7.1 /3.3 | 4.9 /2.2 | 2.7 /0.9 | 1.2 /0.6 | 0.3 |
| Pro. Time (Sec.) | 11.5 /11 control | | 10.5 /11.5 | | | | | |
| TP/Albumin (gm.%) | 7.2 /4.4 | | 6.5 /3.3 | | | | | |

HAA Negative
Alpha Fetoprotein Negative

Oxymethalone 200 mg./d
1/73 → 1/74    4/74 → 6/5/75
↑
Liver Biopsy
6/9/76

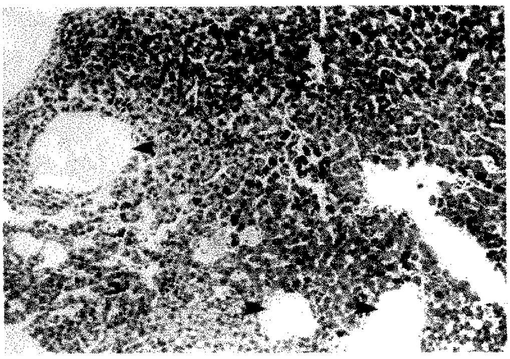

Fig. 1—Percutaneous liver biopsy. There are many peliotic lesions of varying sizes (arrows) most of which appear to communicate directly with sinusoids. Red blood cells have been washed out of all but two small lesions during fixation and mounting of the biopsy (Masson trichrome, original magnification x40).

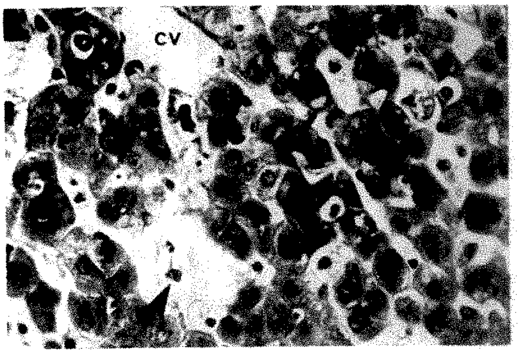

Fig. 2—Percutaneous liver biopsy. Pericentral area demonstrating bile plugs in dilated canaliculi and an early peliotic lesion below the central vein. Ghostlike remains of necrotic hepatocytes are still visible in this early lesion. Arrow indicates a cell ghost within a peliotic lesion. CV = central vein (Masson trichrome, original magnification x310).

Intermittent atrial fibrillation had occurred since 1962, responding to digoxin and quinidine. Bilateral solitary renal cysts were noted in 1972. He denied a history of gallstones, pruritus, recent abdominal pain or change in stool color, although his urine had darkened over the 48 hours prior to admission. Physical examination revealed a grossly jaundiced male in no distress. Blood pressure was 180/90, vital signs were otherwise unremarkable. Liver edge was felt three fingerbreadths below the right costal margin and was slightly tender, with a total liver span of 16 cm. The spleen was not palpable and stool was guaiac negative. There was 2+ pitting edema of the lower legs. A technetium sulfur-colloid liver spleen scan showed a diffusely enlarged liver with minimally decreased overall activity. The spleen was normal in size. Liver studies at admission revealed a bilirubin of 7.1/3.3 direct; SGOT, 53; SGPT, 97 and an alkaline phosphatase of 2.5 (Table I). Oxymetholone therapy was discontinued.

On 9 June 1975, he underwent percutaneous aspiration needle liver biopsy without complication. The biopsy specimen (Figs. 1 and 2) revealed marked cholestasis, focal hepatocellular necrosis and many blood filled cystic areas of varying size consistent with peliosis hepatis. Phenobarbital, 30 mg. p.o., q.i.d. and prednisone, 60 mg./day were instituted, the latter medication for treatment of nephritis. Bilirubin and transaminases returned to normal over a two-month period and the patient felt well. Sputum cultures for mycobacterium tuberculosis obtained May, 1975, were reported as positive July, 1975 and he was begun on ethambutol and rifampin.

## COMMENT

Earlier literature described peliosis hepatis in association with tuberculosis and disseminated malignancy.[5, 6] More recently its occurrence has been noted in patients receiving anabolic-androgenic steroids[1, 7, 8] (testosterone enanthate or proprionate, methyltestosterone, oxymetholone, fluoxymesterone, methandrostenolone, norethandrolone, nandrolone decanoate), oral contraceptive agents[9] (norethindrone with mestranol—Ortho-Novum), and estrogenic hormones[3] (estrone sulfate—Premarin).

A recently published series[4] described the first well documented case of histologic regression of the peliotic lesion. Although such proof would have been desirable in our case, repeat liver biopsy was not performed for obvious ethical reasons. The patient's rapid clinical and biochemical improvement following oxymetholone withdrawal, prior to the institution of antituberculous therapy, suggests that his hepatic lesion was related to the androgenic agent.

Although needle liver biopsy presents the theoretical risk of hemorrhagic complications, none have been reported to date as a result of this procedure. Early investigation is warranted for patients who develop hepatic dysfunction (usually a cholestatic picture) and/or hepatomegaly while taking any of the above-noted medications. Discontinuation of the drug may be followed by rapid clinical improvement, as in our case.

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*Clinical Vignette*

# Massive Rectal Bleeding Due to Intestinal Tuberculosis

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Two cases of massive rectal bleeding due to tuberculosis of the intestine are described and 24 reported cases of massive rectal bleeding in intestinal tuberculosis are reviewed. Tuberculosis of the intestine, though uncommon should be considered as a cause for rectal bleeding.

Tuberculosis of the intestine is still common in developing countries. Most patients present with obstructive symptoms or an alteration in the bowel habit[1] and some present with perforation of bowel.[2, 3] Massive bleeding per rectum, however, is a rare menifestation of the disease. This report concerns two patients in whom this complication occurred.

## CASE REPORTS

*Case 1:*—M. K., a 20-year old married female, was admitted to the All India Institute of Medical Sciences Hospital with complaints of low grade fever for 10 months, along with cough and intermittent attacks of abdominal pain associated with vomiting and distention for five months. She was ill nourished and pale, febrile and dehydrated. There was diffuse tenderness over the abdomen and pedal edema was present.

Laboratory investigations disclosed hemoglobin of 7.3 gm./dl. and an erythrocytic sedimentation rate of 30 mm./hr. X-ray of the chest revealed a healed parenchymal lesion in the left mid zone and calcified lymph nodes in the hilar region. Barium studies showed a contracted cecum and a constricted ileum. On the ninth day after admission, massive bleeding occurred per rectum. Four days later, there were three other large bleeding episodes, consisting of passage of dark red blood. The pulse rate rose to 140/min. and systolic blood pressure declined to 50 mm. Hg. Transfusion of five units of blood was instituted and an emergency laparotomy performed.

Localized, whitish, nodular areas were seen in the terminal ileum and in the proximal ileum. The small bowel was not dilated proximally, The colon was filled with blood and the mesenteric lymph nodes were enlarged and fleshy. Ileal resection and right hemicolectomy were performed. The postoperative period was uneventful. The histological report was tuberculous enterocolitis with multiple ulcerations.

*Case 2:*—A. K., a 22-year old male student, was admitted to the All India Institute of Medical Sciences Hospital with complaints of severe bleeding per rectum of eight hours' duration. He had a two-year history of occasional loose movements and

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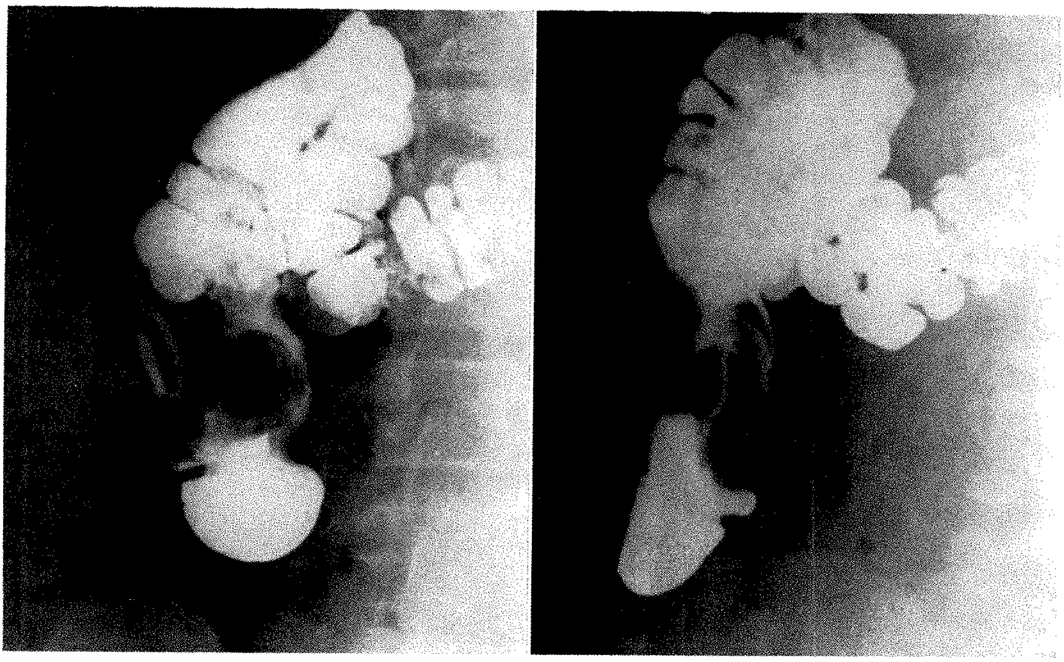

Figs. 1 and 2—Barium meal study (Case 2) showing a lobulated filling defect in the region of the ascending colon with ulceration.

mild abdominal discomfort for which he had not consulted a doctor.

He appeared pale, had pulse rate of 108/min. and a blood pressure of 110/70 mm. Hg. Abdominal examination was negative. Rectal examination revealed dark red blood on the examining finger.

Hemoglobin was 10.8 gm./dl. and the erythrocyte sedimentation rate was 44 mm./hr. Endoscopy revealed a normal gastrointestinal tract. Chest x-ray was normal. Emergency superior mesenteric angiography revealed an area of doubtful abnormality in the cecum. Subsequent barium meal study showed a lobulated filling defect in the region of the ascending colon with ulceration, suggestive of space-occupying lesion of the ascending colon, probably leiomyoma (Figs. 1 and 2). Barium enema study revealed an area of narrowing of the ascending colon with spiky outline. The cecum showed loss of haustrations and the possibility of involvement of the ileocecal region and of the proximal ascending colon was also entertained (Fig. 3).

Five large bleeding episodes occurred within 18 hours after admission. The bleeding stopped spontaneously the day after admission and the general condition of the patient improved. Elective surgery was performed three weeks later. At laparotomy he was found to have an ulcero-constrictive lesion in the cecum for which right hemicolectomy was done. The immediate postoperative period was uneventful. The histopathological report was of tuberculous enteritis of the ileocecal region.

## COMMENT

Though minor rectal bleeding in tuberculosis of the intestine has been described fairly frequently[1, 4-7] massive

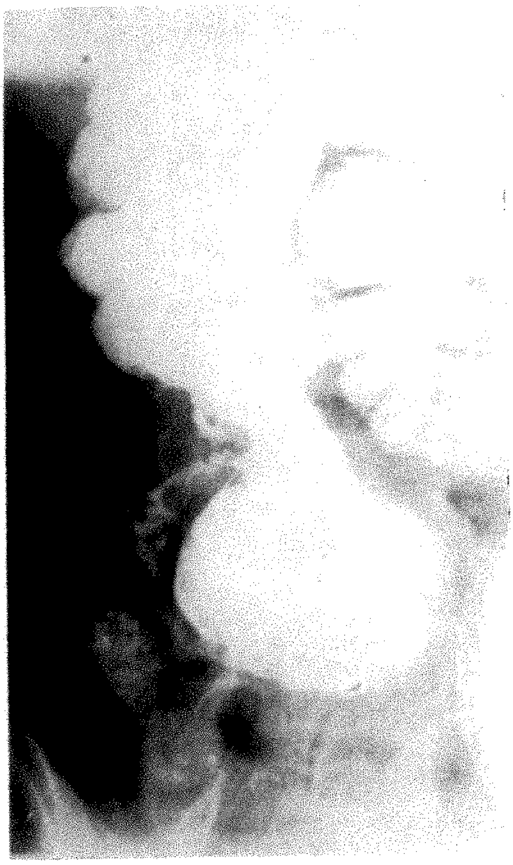

Fig. 3—Barium enema study (Case 2) showing an area of narrowing of the ascending colon with spiky outline and loss of haustrations of the cecum.

hemorrhage per rectum necessitating blood transfusion or urgent operation is very rare. Anscomb, et al[8] reported nine cases of cecal tuberculosis, of which two had massive bleeding per rectum. Brenner, et al[9] reported one case of tuberculous colitis who presented with a history of passing bright red blood per rectum, there was no other clinical evidence of intestinal tuberculosis. Olavi, et al[10] found only one instance of profuse hemorrhage from a jejunal tuberculous ulcer in 36 cases of intestinal tuberculosis.

Both of our patients were young, 20 and 22 years, respectively. One was a woman (Case 1) and the other a man (Case 2). Both presented with severe bleeding per rectum. The woman patient had a healed tuberculous lesion in the lung and associated symptoms of subacute intestinal obstruction. A preoperative diagnosis of intestinal tuberculosis as the cause of rectal bleeding was possible. The young man, however, presented with massive bleeding per rectum without associated symptoms or prior illness to suggest tuberculosis of the cecum.

It is suggested from our experience with these two patients, that tuberculosis of intestine though uncommon should be kept in mind as a cause for rectal bleeding.

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***Clinical Vignette***

# Absorption of Orally Administered Digoxin After Massive Resection of the Small Bowel

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Digoxin absorption was studied in a patient after massive small bowel resection (with only 15 cm. of jejunum left) after mesenteric thrombosis. Oral administration of 0.25 mg. digoxin tablets resulted in therapeutic blood levels between 0.7 and 2.2 ng./ml. Measurement of the urinary excretion of the drug in steady state revealed more than 80% of the maintenance dose. Renal digoxin clearance was 125 ml./min. This resulted in slowing of the heart rate from 120 to 80/min. with no side-effects. It is thus concluded that total absorption of digoxin might be normal in a patient with only 15 cm. of jejunum and that usual dogs of digoxin were sufficient for a therapeutic effect and "therapeutic" blood levels.

The gastrointestinal absorption of digoxin in man has been estimated by several authors.[1-4] The sites and mechanisms of digoxin absorption are not fully known. About 85% of the drug is bioavailable from the best absorbable oral formulation.[5] Some absorption of the drug takes place from the stomach but gastric absorption appears to be of minor importance.[6-8] Absorption of radioactive digoxin was compared to polyethylene glycol (a nonabsorbable marker) and it was found that about 60% of the radioactivity was absorbed from the upper gastrointestinal tract.[4] These observations were carried out in normal individuals with an inact gastrointestinal tract or in patients after gastric operations.

Orally administered radioactive compounds may be degraded within the intestine so that absorption of the label may not necessarily correspond to that of the drug. Moreover, digoxin absorption was found to be decreased in patients with malabsorption syndromes.[9]

We have studied the absorption of digoxin and its clinical effect in a patient with only 15 cm. of jejunum remaining after massive resection of the small bowel because of mesenteric artery thrombosis. The adequate plasma levels and urinary excretion of digoxin indicate that the drug is mainly absorbed through the remaining portion of the gut.

## CASE REPORT

A 77-year old male was admitted to the Hadassah University Hospital because of abdominal pain, vomiting and bloody diarrhea, which started one day prior to admission. The patient was known to suffer from hypertensive and ischemic cardiovascular disease with cardiac dysrhythmias and peripheral vascular disease. He was treated with Quinidine, dipyramide and chlorthiazide. On examination he was cold and sweating. The blood pressure was 180/100 and the pulse rate 90/min., full and regular. Crepitations were heard over both lung bases. Heart sounds were normal and there were no murmurs. The abdomen was soft with diffuse tenderness but no signs of peritoneal irritation. Peristalsis was present. Rectal examination was negative and rectal temperature was 37.5° C. Urinalysis was normal. Hemoglobin was 13.3 gm./dl. White count was 11,300/cu. mm. Blood urea nitrogen, glucose, electrolytes, diastase, proteins and bilirubin were within normal limits. Alkaline phosphatase was 110 units (normal less than 80) and SGOT was 75 units (normal less than 50). The electrocardiogram showed first degree A-V block, right bundle branch block, left anterior hemiblock and diffuse ST-T changes. There were frequent supraventricular extrasystoles. Plain abdominal x-rays showed a single distended loop of bowel in his left abdomen. Barium enema and rectoscopy were negative.

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No definite diagnosis was made and the patient was admitted for further observation. On the third day the patient experienced an acute attack of severe abdominal pain with profuse sweating. The blood pressure rose to 200/100 and there was tachycardia of 120/min. Abdominal distention became evident with tenderness and rigidity, especially on the left side. No peristaltic sounds were audible. Mesenteric vascular occlusion was suspected and an immediate laparotomy was performed. At operation, thrombotic occlusion of the superior mesenteric artery with severe ischemia of the bowel was encountered. Endarterectomy and patch grafting was unsuccessful since free outflow tract could not be established. An ischemic demarcation line appeared in the proximal jejunum, 15 cm. from the ligament of Treitz. The compromised bowel extended up to the mid transverse colon. The ischemic bowel was resected and an end-to-end jejunocolic anastomosis performed. Several attempts to feed the patient with various regimens including elemental diet resulted in severe diarrhea and weight loss. Simple tests of intestinal function showed a normal xylose absorption but only 40% absorption of an administered dose of amino acid supplement (amigen) as calculated from fecal nitrogen excretion.

Intravenous hyperalimentation was instituted via a specially introduced subclavian catheter. After three months the patient developed atrial fibrillation with a ventricular response of 120/min. Since there was also trifascicular block, slow digitalization was commenced by 0.125 mg. for two days, followed by 0.25 mg. oral tablets. Serum digoxin levels and urinary excretion determined by radioimmunoassay[10] are shown in Figure 1. The patients' serum levels during maintenance therapy with oral 0.25 mg. of digoxin were within the expected therapeutic range (0.8-2.2 ng./ml.). Measurement of the urinary excretion of the drug (in steady state) revealed more than 80% of the maintenance dose. Renal digoxin clearance was 125 ml./min. Thus therapeutic levels of digoxin were achieved in spite of resection of most of the small bowel. The heart rate slowed to 80/min. and there were no side-effects. The patient lived for five months and suffered from several episodes of Candida sepsis which responded to treatment with 5 fluoro-cytosine and amphotericin B. The patient died of catheter sepsis. Postmortem examination was refused.

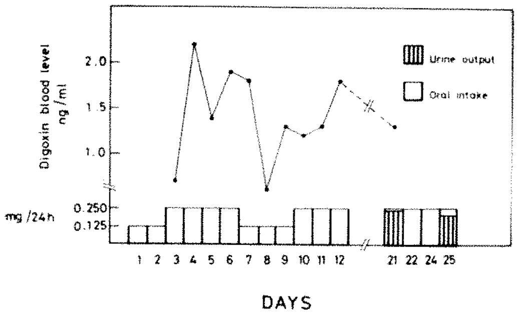

Fig. 1—Blood levels of digoxin and urine output in a patient with only 15 cm. of jejunum after extensive small bowel resection.

## COMMENT

Measurement of the concentration of digitalis compounds in body fluids has elucidated the pharmacokinetics of the cardiac glycosides.[11-13] A wide range (40-85%) of absorption of oral digoxin has been reported in the literature.[2-4, 14] Since the drug is excreted primarily by the kidneys the serum half-life is dependent primarily on renal function.[15] The cumulative urinary excretion of orally administered digoxin varies between 43-62%. The total amount of the drug absorbed is probably higher, however, than that eliminated in the urine since some 10-30% is excreted in the bile and undergoes an enterohepatic circulation.[3, 16, 17] Thus neither urinary nor fecal elimination of the glycoside or its metabolites truly reflects the absorption of digoxin. After administration of $H^3$-digoxin, about 60% of the radioactivity is absorbed from the stomach, duodenum and upper jejunum. Some additional radioactivity is absorbed from the lower part of the small intestine.[4] Recently Ochs, et al[8] injected digoxin solution into the transverse colon in patients undergoing colonoscopy and found a delayed but quite extensive absorption. Interpretation of this data may be further complicated by degradation of labeled digoxin prior to absorption so that measurement of radioactivity may not correspond to the whole glycoside molecule. Heizer, et al[9] studied serum levels of digoxin in patients with marked steatorrhea due to sprue, pancreatic insufficiency, hyperosmolality and small bowel resection. The subjects received 0.25 mg. digoxin/day and steady state of levels were reached after six days. Whereas the concentration in control subjects averaged 1.3 ± 3 ng./ml., the values for patients with malabsorption ranged between 0.2-0.7 ng./ml.

Beerman, et al[7] found no impairment of absorption of digoxin from the upper gastrointestinal tract in patients with gastric resections. On the other hand intestinal absorption and urine excretion of digoxin in a patient with jejunocolostomy were markedly reduced.

Normal therapeutic plasma levels and urinary excretion of digoxin attained by oral intake in a patient with resection of most of the small bowel was to our knowledge not previously reported. Beerman, et al[7] showed diminished digoxin absorption and urinary excretion in a patient with small bowel resection and jejunocolic anastomosis. Heizer, et al[9] showed a decreased steady state digoxin level in a patient with small intestinal resection and mesenteric vascular insufficiency, although in this case the amount of resection was not stated. Both of these patients had significant malabsorption of digoxin due to impaired bioavailability secondary to a shortened transit time. The absence of any oral intake apart from digoxin in our patient on parenteral hyperalimentation may have sufficiently prolonged the transit time of digoxin so that it could be completely absorbed. Marcus, et al[18] have shown that digoxin absorption proceeds normally in seven patients after jejunoileal by-pass surgery. The high percentage of maintenance dose excreted in the urine is further evidence for increased absorption. The expected cumulative urinary excretion is 60% of the maintenance dose[17] whereas in our patient it was above 80%. Diminished biliary excretion of digoxin may have also been a contributory factor.

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# State of the Art*

## THE TRAINING OF A GASTROINTESTINAL ENDOSCOPIST

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Gastrointestinal endoscopy is an invasive technic for the diagnosis and treatment of disorders of the alimentary tract. It permits visual and physical access to the mucosal surface of those segments of the gut which are within reach of the modern endoscopes and (laparoscopy) to certain of the viscera which are located within the peritoneal cavity. Hollow metal tubes and fiberoptic instruments are used for this purpose. The former have long been employed for esophagoscopy, proctosigmoidoscopy and peritoneoscopy; the latter, more recently developed ones, for esophagogastroduodenoscopy, for providing access to the duodenal papilla and pancreaticobiliary ductal system and to the entire colon and distal ileum.

Featured by great flexibility, patient acceptance and diagnostic and therapeutic capabilities, the fiberoptic instruments have exerted a profound impact on gastrointestinal endoscopy, expanding its applicability and increasing its attractiveness.[1] They are used not only by gastroenterologists and alimentary tract surgeons but by other surgical and nonsurgical practitioners as well. Included among these are internists, radiologists, family practitioners, general surgeons, gynecologists, thoracic surgeons and otolaryngologists.

Unfortunately, technological advances in the development of endoscopic instruments have occurred at too rapid a pace. At the present time, there exists a significant deficit in the number of individuals who possess the qualifications to use them properly. Hopefully, expansion of well-conducted training programs in gastrointestinal endoscopy will resolve the dilemma created by the poorly trained individual and, by satisfying the need for endoscopists, serve to dissipate the unwholesome aura which has developed, relating to excessive fees and excessive utilization of the various procedures. These factors succeed only to cast discredit upon the method[2,3] and efforts which seek to place the matter into proper perspective[4] are rewarded by scoffing replies.

The training of a gastrointestinal endoscopist requires that he become skilled in the technics for manipulating those instruments which he elects to employ, proficient in interpreting the observations which they provide and capable to perform all of the established diagnostic and therapeutic procedures which they permit. Each of these factors is extremely important; as much harm may be visited upon a patient in consequence of faulty interpretation as from traumatic perforation. To this end, the trainee must learn the appearance of the normal and pathologic anatomy and physiology of those structures which his instruments traverse, the disease states which affect them and the interpretation of gastrointestinal radiographic films. The importance of the latter cannot be overly emphasized: endoscopy and radiography are mutually complementary procedures, not exclusive or antagonostic.

The trainee must be taught the capabilities and the limitations of those endoscopic procedures which he performs, as well as the correct timing of their application in relation to the development of a clinical problem. He also must be made acutely aware of the indications and contraindications to their use and of the hazards and cost, in relation to the benefit which they may be expected to provide, when utilized in any given case. This will enable him to impart to his patient the information which is legally required for obtaining valid consent for endoscopic examination and will help to avoid over-utilization of the procedures.

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* Edited by Walter Harvey Jacobs, M.D., F.A.C.G.

How is endoscopic competence acquired? The early endoscopists, for the most part and of necessity, were self-taught. For many, the introduction to the method involved understudying Dr. Rudolf Schindler, in Chicago, usually for a short period of time and subsequently returning home to perform the procedure on their own. This closely knit cadre of aficionados actively exchanged the endoscopic observations and experiences which they derived from the examinations which they performed on their patients. They constructed the foundation for the science of gastrointestinal endoscopy and initiated the establishment of training programs in endoscopy in their institutions. These individuals and their trainees experienced little difficulty in adapting to the transition from the use of lensatic instruments to that of the fiberoptic ones. Similarly, those, whose initial exposure to gastrointestinal endoscopy occurred during the era of the upper gastrointestinal fiberoptic instruments, rapidly acquired the expertise required for the developments which occurred subsequently—colonoscopy and endoscopic retrograde cholangiopancreatography.

Thus, it is possible for certain individuals to attain competence in endoscopy, by following the self-teaching, or "do-it-yourself" route and in the absence of formal instruction. This path, however, is fraught with hazards to the welfare of the patient and presents serious pitfalls and hardships to the traveler. This fact has been impressed, by tragic experience, upon certain naive persons who have permitted themselves to be deluded by the relatively innocuous appearance of the instruments and the appearance of simplicity of the method. A recent survey of colonoscopy has indicated that the risk of minor and major complications from this procedure may be as high as 5% of cases, in the hands of the inexperienced endoscopist. The insistence by qualified endoscopists upon the necessity for adequate training of those who wish to engage in the practice of this expertise, is not predicated upon the "haves versus the have-nots", nor upon socioeconomic considerations. It is based upon the absolute necessity for protecting the patient and for preventing the method from falling into disrepute.

The *compleat* gastrointestinal endoscopist is expert in the performance of all of the procedures which were previously enumerated and several ways exist by which a physician may attain such proficiency. Ideally, this will derive from his participation, for a period of one or two years, in an approved training program in surgical endoscopy or in gastroenterology. There he will obtain formal, practical and in depth instruction in each type of gastrointestinal endoscopic procedure, commonly provided on a preceptorship (one-to-one) basis. This type of indoctrination is suited to the young physician (PG 3 and 4) who participates in a training program in gastroenterology or surgery that includes the teaching of gastrointestinal endoscopy.

## TRAINING PROGRAMS

The necessary requirements of training programs in gastrointestinal endoscopy were outlined by the American Society for Gastrointestinal Endoscopy in response to a multitude of requests from hospital directors for guidance in the matter of determining who could do endoscopy in their institutions. The guidelines which eventuated represented the product of the expenditure of much thought and effort by many accomplished endoscopists experienced in the teaching and practice of this subject.[5] In essence, they included most of the following recommendations:

The training director in endoscopy must be a skilled and highly qualified endoscopist. He must exercise close and immediate supervision of the performance of scheduled and emergent procedures by the trainees and this must continue until such time as they demonstrate the attainment of competence in endoscopic technic and interpretation. When the endoscopic training director is not the program director, he must be given the ultimate authority and responsibility to determine whether and when the endoscopic trainee is qualified in the performance of the specific endoscopic procedures.

The trainee must be afforded a broad exposure to the best available endoscopic instruments and accessories for each of the procedures which he is being taught—esophagogastroduodenoscopy, colonoscopy, ERCP, laparoscopy. Knowledge of the technical and mechanical features of the equipment, its maintenance and cleaning and of the measures required to protect it from malfunctioning or breaking during use, is essential before clinical utilization is attempted. Similarly, instruction in the technics and fundamentals of biopsy, cytology and photography must be given to the trainee before he attempts its clinical application.

For each endoscopic procedure to be learned, the pertinent literature and teaching aids, (such as mannequins, motion pictures, transparancy files and videotape presentation on technic) should be studied by the trainee.

The degree of endoscopic competence which an individual acquires during his training is distinctly related to the number of procedures which he performs. Endoscopic training programs must provide the quantity of clinical material which is required to produce competent endoscopists. Since, as has been mentioned, individual abilities and skills vary greatly, recommendations for adequacy of endoscopic training must, perforce, be flexible. For each trainee, the judgment and discretion of the training director in endoscopy must establish the point in time when he has attained the necessary degree of competence to be permitted to perform a given endoscopic procedure on his own.

The ASGE guidelines arbitrarily recommend the performance by the trainee, as primary endoscopist, of a specific number of each type of procedure before being permitted to perform them on his own:

Upper gastrointestinal panendoscopy:
100 cases as primary endoscopist
Colonoscopy:
50 ” ” ” ”
Polypectomy:
25 ” ” ” ”
ERCP:
25 ” ” ” ”
Laparoscopy:
25 ” ” ” ”

This recommendation has drawn severe criticism from a few Gastroenterology Training program directors who assert that their training programs are incapable of providing the recommended number of endoscopic procedures for each trainee and who voice the fear that, in consequence, the trainees may become involved in performing unnecessary procedures in order to fulfill the requirement of numbers. This criticism is totally unfounded. One of the most important functions of an endoscopic training director is to teach to the trainee in endoscopy the indications and contraindications for a procedure—and to insure that this requirement is complied with. Furthermore, the number of trainees in a given program must be determined by the ability of that program to provide adequate training and adequate clinical case material.

The trainee must be instructed in endoscopic photography and learn to document his findings by this technic. The photographs should be reviewed with his supervisor.

In addition to his training in endoscopy, correlation between endoscopic interpretation and other diagnostic modalities, including x-ray and pathologic studies, must be included in the experience provided to the trainee. A close professional relationship between the supervisor and trainee is required during the period in which the latter develops into an experienced endoscopist.

There exist other groups of physicians who wish to obtain training in gastrointestinal endoscopy but for whom full-time participation in a prolonged period of formal training of the type described is not feasible or is more extensive than required or desired. Included among these are individuals who are established in the practice of medicine and who find it impossible to revert to the status of a Resident or Fellow in order to obtain endoscopic training. Others may wish to develop proficiency in only one type of gastrointestinal endoscopic procedure. Again, there exists the physician who received adequate training in upper gastrointestinal endoscopy sometime in the past and now wishes to master the diagnostic and therapeutic technics of the methods which proliferated subsequently (colonoscopy and ERCP).

A more limited and specific type of training should be adequate to satisfy the requirements of these individuals. It should include the development, on an apprenticeship basis, of practical experience in performing the specific procedures in conjunction with comprehensive study. The former involves a period during which the trainee observes the performance, by a competent endoscopist, of the procedure which he wishes to learn; subsequently he performs the recommended number of procedures himself, under the direction of his chosen mentor. In this regard, the ethical and medico-legal considerations are paramount and must be satisfied. Practical experience, much less satisfactory in nature, is also attainable through participation in short courses which are provided at certain institutions. Practical experience must be supplemented with intensive study utilizing audio-visual aids and the pertinent literature. Also of limited value to the trainee is attendance at didactic courses related to the particular aspect of gastrointestinal endoscopy which is of interest to him. These are presented at various locations, periodically. They generally include in their faculty, a few recognized endoscopists who are drawn from the local community, and one or more itinerant guest lecturers. The latter are selected from a cadre of individuals who possess the inclination and the time to travel extensively for the purpose of disseminating endoscopic expertise.

In essence, therefore, the physician who has been adequately trained in gastrointestinal endoscopy has been endowed with highly specialized skills which are not possessed by his nonendoscopist colleagues. In his management of patients, whether referred or his own, he alone must decide upon the necessity for performing an endoscopic procedure, which procedure is indicated, the type of instrument and medication which should be used, etc. He accomplishes this in the context of his personal evaluation of a given patient and of the nature of the clinical problem which is presented. Thus, the gastrointestinal endoscopist functions as a consultant. To designate him a "technician," as some have done, is erroneous and demeaning. Furthermore, any suggestion that the performance of gastrointestinal endoscopic procedures may be relegated to paramedical personnel, as also has been made, is irresponsible and dangerous.

The goal of endoscopic training is to impart, to the student, all aspects of endoscopic training, the assimilation of which will result in a safe procedure with an accurate and effective interpretation.

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# The Radiology Corner*

## COLONIC INTUSSUSCEPTION IN UREMIA

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Colonic intussusception is a condition primarily found in infants and young children. In adults, it is usually associated with a colonic neoplasm. The following report illustrates a case of colonic intussusception in an adult uremic patient in whom postmortem examination showed evidence only of intramural colonic hemorrhage.

### CASE REPORT

The patient was a 35-year old black male admitted because of cough and dyspnea of one day's duration. He gave a history of hypertension for five years. On admission the blood pressure was 210/160. The heart was enlarged and there was evidence of left heart failure with rales and rhonchi. The BUN was 128 mg./dl. and the creatinine 14.9 mg./dl. The patient was treated for heart failure with diuretics and for hypertension with Aldomet®. The uremia was treated by a low protein, low sodium diet with Kayexalate®.

One month after admission, the patient developed abdominal pain and rectal bleeding with a drop of the hematocrit to 17. This required seven transfusions of 250 ml. each of sedimented cells. During the course of hospitalization the BUN rose to 240. A barium enema was performed seven days after the onset of the abdominal pain and rectal bleeding. The study showed evidence of intussusception in the proximal transverse colon (Figs. 1 and 2). After the barium enema, there was minimal improvement in the patient's abdominal symptoms. Seven weeks after admission and eight days after the performance of the barium enema, the patient developed sudden severe chest pain and expired.

At autopsy, the kidneys were markedly reduced in size and there were microscopic changes consistent with chronic diffuse pyelonephritis. The heart showed acute fibrinous pericarditis with marked hypertrophy of the left ventricle. There was intussusception of the cecum into the transverse colon which was easily reduced. There was no evidence of neoplasm in the colon. There were, however, scattered hemorrhagic areas, areas of ulceration and diffuse marked submucosal edema.

### COMMENT

In contrast to primary or idiopathic intussusception that occurs in the infant and young child, intussusception in the adult is almost always associated with a localized lesion.[1] The most common underlying pathology is a tumor, a polyp or an inflammatory lesion.

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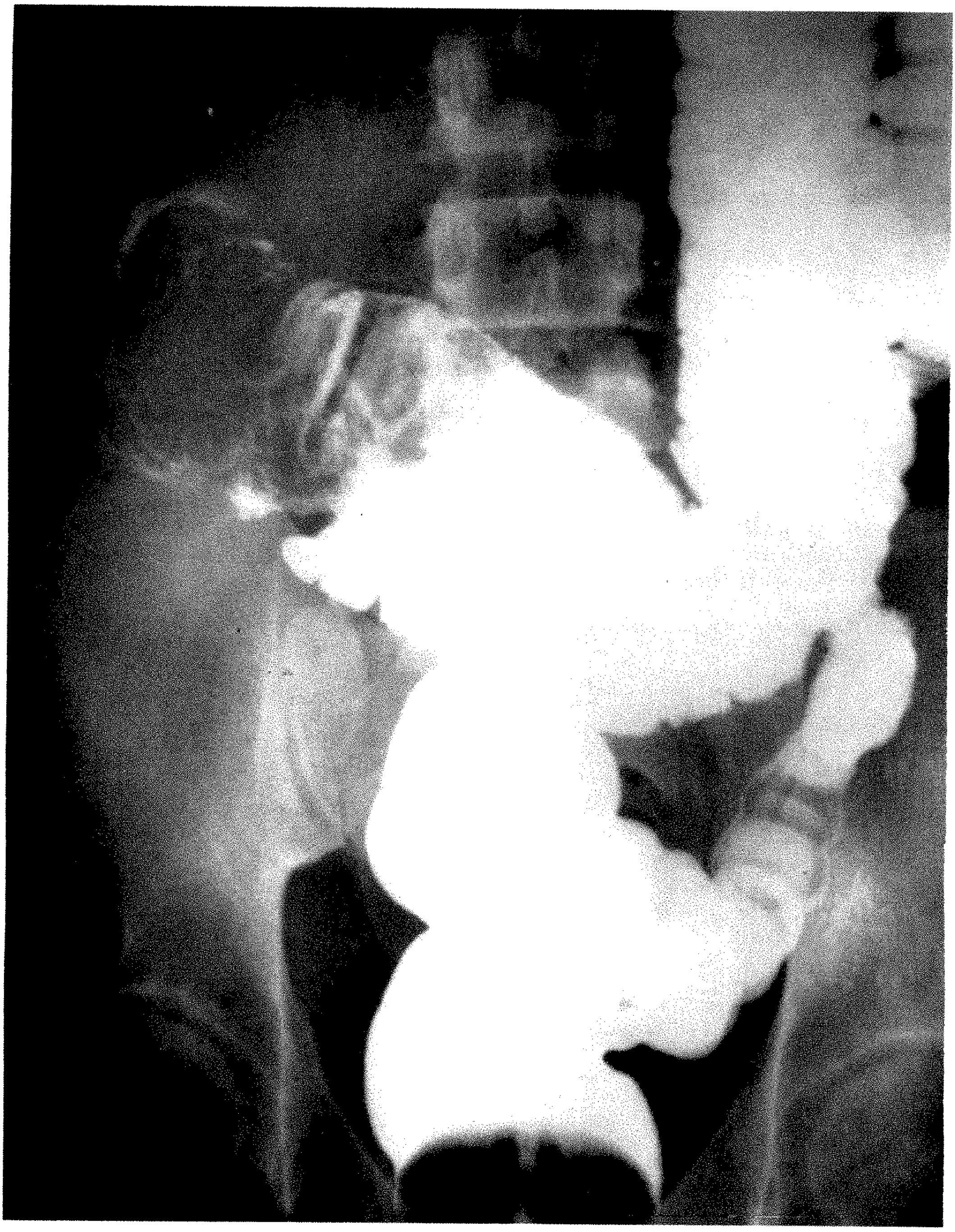

Fig. 1—Barium enema, filled roentgenogram. There is complete retrograde obstruction to the flow of barium in the proximal transverse colon with the barium surrounding a tubular filling defect.

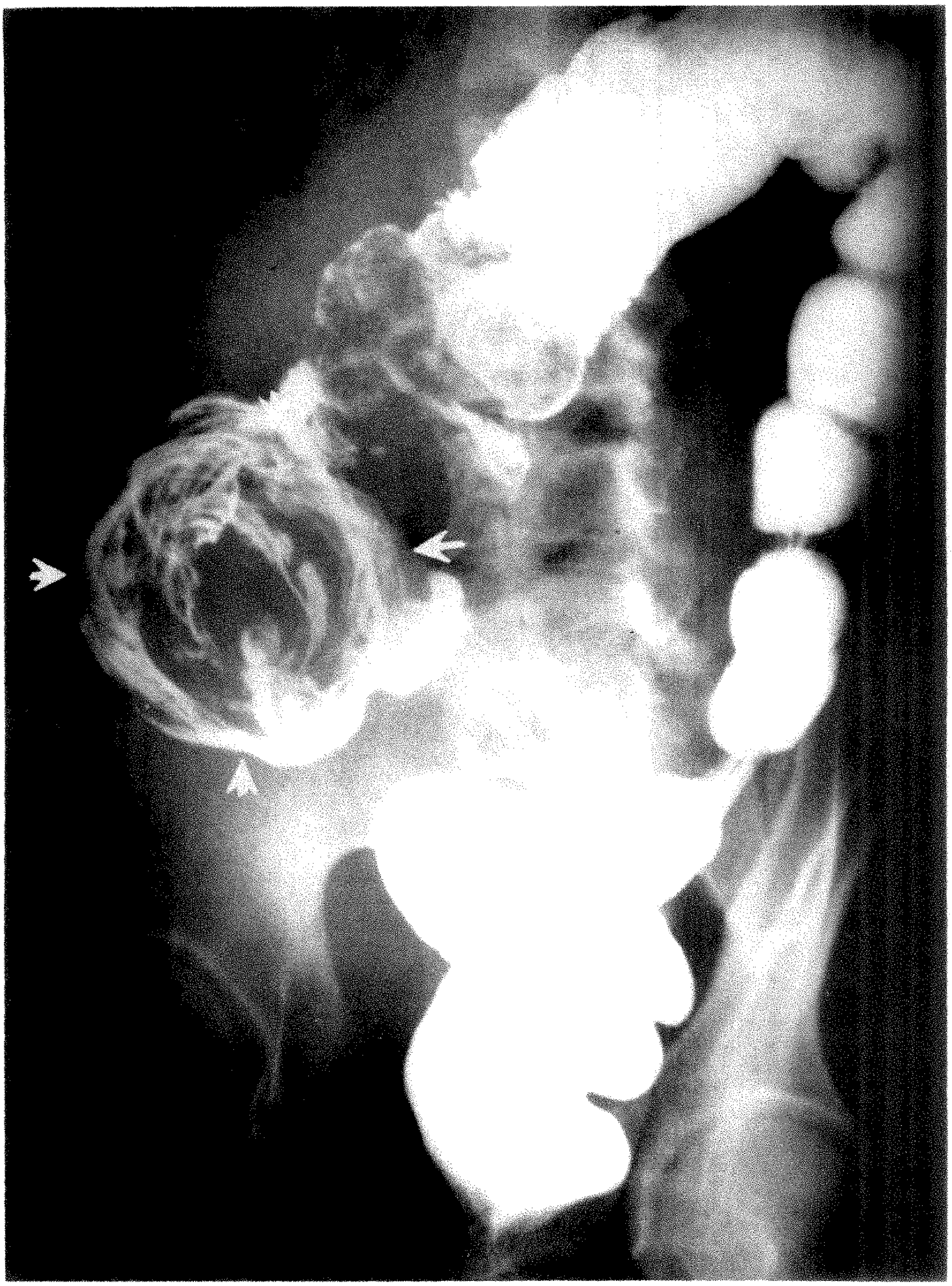

Fig. 2—Barium enema, postevacuation roentgenogram. The coil-spring pattern surrounding the intraluminal filling defect is characteristic of intussusception (arrows).

Roentgenologic diagnosis of intussusception on the plain film of the abdomen may be difficult, although the presence of a soft tissue mass protruding into the lumen of the gas filled distal bowel is suggestive of this diagnosis. Barium enema examination is necessary for confirmation of the diagnosis. This study reveals a concave or a cup-shaped abrupt termination of the barium column at the site of the leading head of the intussusception. Further, demonstration of a characteristic coil-spring pattern may be evident as the barium flows between the intussusception and intussuscipiens (Figs. 1 and 2).

The occurrence of intestinal intussusception resulting from intramural bowel hemorrhage is well documented in patients with Henoch-Schonlein's purpura, leukemia and in patients receiving anticoagulant therapy.[2] Carl, et al[3] first reported bowel intussusception in chronic renal failure in 1976. This was believed to be a sequel of intramural bowel hemorrhage resulting from the coagulopathy related to platelet dysfunction in uremia, whereby an intramural hemorrhage formed the nidus for the development of intussusception. Postmortem examination in our case, similarly, showed no etiology of the intussusception other than hemorrhagic areas in the wall of the cecum. With the increased survival of uremic patients as a result of dialysis and renal transplantation, this etiology of colonic intussusception may become more common. It should be considered in the differential diagnosis of abdominal pain in uremic patients.

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# The Last Page

## QUESTIONS IN GASTROENTEROLOGY

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*The Last Page* appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the article can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. LOWER ESOPHAGEAL SPHINCTER PRESSURE AND REFLUX AFTER FUNDOPLICATION:

   A. All patients with low preoperative LESP increased it by at least twice after Nissen fundoplication.

   B. Reflux demonstrated by pH probe does not disappear postoperatively.

   C. Symptoms and endoscopic esophagitis disappeared postoperatively.

   D. Postoperative "gas bloat" syndrome is treated with dilatation.

   (Page 154)

2. HEPATITIS B ANTIGEN AND ANTIBODY IN HEROIN USERS:

   A. There is an increased incidence of both Type B hepatitis and asymptomatic $HB_s$-Ag carrier state in heroin users.

   B. Intravenous and nonparenteral users of heroin among US soldiers in Vietnam had the same incidence of $HB_sAg$.

   C. Hepatitis B virus is spread solely by parenteral route.

   D. The lower incidence of antibody to HBs in nonparenteral users is due to their shorter duration of exposure.

   (Page 164)

3. WITH ULTRASONOGRAPHY IN CHOLESTATIC JAUNDICE:

   A. Dilatation of the intrahepatic bile ducts is found in approximately 90% of cases of extrahepatic obstruction.

   B. Dilatation of the common bile duct can be shown as frequently.

   C. No cases of intrahepatic cholestasis showed dilated ducts.

   D. When no dilated ducts can be found ERCP should not be performed.

   (Page 168)

4. CRST SYNDROME, PROGRESSIVE SYSTEMIC SCLEROSIS AND THE PANCREAS:

   A. The full CRST syndrome occurs in less than 5% of patients with progressive systemic sclerosis.

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B. Diabetes, steatorrhea and pancreatic enzyme deficiencies have been associated with systemic sclerosis.

C. Chronic calcific pancreatitis does not occur in this syndrome.

D. Abdominal pain is never due to pancreatitis in systemic sclerosis.

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5. PANCREATIC POLYPEPTIDE AND GLUCOSE ADMINISTRATION:

A. In the dog PP acts on the gut, pancreas and gallbladder.

B. Oral glucose in man is followed by a rise in serum PP concentration.

C. Intravenous glucose in man is followed by a similar rise in PP.

D. Glucose has no effect on PP release from the isolated perfused dog pancreas.

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6. PANCREATIC ASCITES:

A. Can occur with acute pancreatitis, ductal rupture or pseudocyst.

B. Contains high levels of amylase but its protein is under 1.5 gm./100 ml.

C. Is due to retroperitoneal obstruction of pancreatic lymphatics.

D. Never resolves on medical treatment.

(Page 186)

7. FOREIGN BODY AS GALLSTONE NIDUS.

A. Pins, bones, sutures and food materal may act as nidi for gallstones.

B. The ova of *Ascaris* are the most common foreign bodies responsible for gallstones.

C. Penetrating abdominal injury may deposit metallic fragments in the gallbladder.

D. Stones forming around such metallic fragments never cause symptoms before 10 years have elapsed.

(Page 193)

8. BCG IMMUNOSTIMULATION TREATMENT OF CROHN'S DISEASE:

A. Thirty per cent of patients with active Crohn's disease had a defect in cellular immunity (DNCB skin test; response to T-cell mitogens).

B. No patients with ulcerative colitis had such defects.

C. BCG stimulates B-lymphocytes.

D. Treatment with oral BCG did not benefit immunodeficient patients with active Crohn's disease.

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9. MEGALOBLASTIC ANEMIA AND CROHN'S DISEASE OF THE STOMACH:

A. Crohn's disease of the stomach always extends into the duodenum.

B. Gastric Crohn's disease causes antral narrowing and spares the upper stomach.

C. Megaloblastic anemia in Crohn's disease is due solely to ileitis with loss of $B_{12}$-intrinsic factor binding sites.

D. Achlorhydria with loss of parietal cells in gastric Crohn's disease is associated with loss of intrinsic factor.

(Page 202)

10. ESOPHAGEAL CARCINOMA COMPLICATING ACHALASIA:

A. Usually occurs late, after an average interval of 17-28 years.

B. Can be diagnosed early clinically and radiologically.

C. Is a common cause of esophagopulmonary fistula.

D. Such a fistula is best diagnosed endoscopically.

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11. DISSEMINATED INTRAVASCULAR COAGULATION IN GASTRIC CARCINOMA:

A. Is more common than in other gastrointestinal tumors.

B. Is more common than microangiopathic hemolytic anemia.

C. Is probably due to release of thromboplastin from the tumor.

D. Is suggested by the presence of "helmet" and "burr" cells on the blood smear.

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12. PELIOSIS HEPATITIS:

A. Is characteristic by blood-filled cystic spaces in the liver.

B. Has been associated with tuberculosis, disseminated malignancy, anabolic-androgenic steroids, oral contraceptives and estrogens.

C. Should never be diagnosed by liver biopsy.

D. Does not regress and is always fatal.

(Page 213)

13. BLEEDING IN INTESTINAL TUBERCULOSIS:

A. Is a fairly frequent manifestation.

B. Is more often massive than minor.

C. Is more common than obstructive symptoms or alteration in the bowel habit.

D. Is always associated with pulmonary tuberculosis.

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14. REGARDING DIGOXIN ABSORPTION:

A. Sixty per cent of radioactive digoxin is absorbed from the upper gastrointestinal tract.

B. Ten to 30% of absorbed digoxin is excreted in bile and undergoes enterohepatic circulation.

C. Digoxin cannot be absorbed from the colon.

D. In a patient with massive small bowel resection leaving only 15 cm. of jejunum, digoxin absorption was inadequate.

(Page 220)

15. COLONIC INTUSSUSCEPTION IN UREMIA:

A. Primary colonic intussusception, without a localized lesion, is as common in the adult as in children.

B. Tumor, polyp or an inflammatory lesion, rather than intramural hemorrhage, are the cause of intussusception in uremia.

C. The diagnosis can be easily made on the plain film of the abdomen.

D. Barium enema reveals a concave or cup-shaped termination of the barium column, or a coil-spring pattern.

(Page 229)

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**WARNINGS:** In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

*Usage in pregnancy:* Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

*Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response.* Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
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Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
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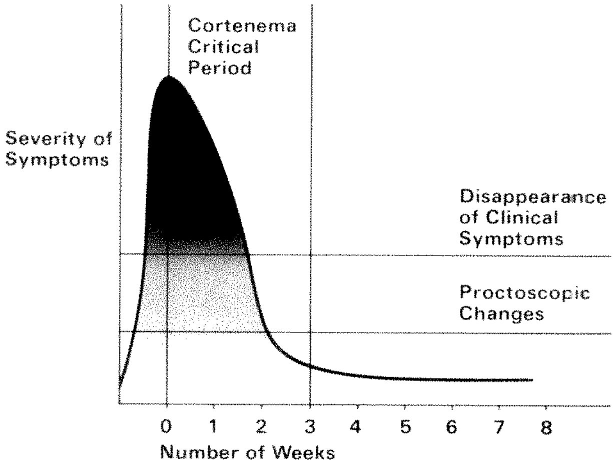

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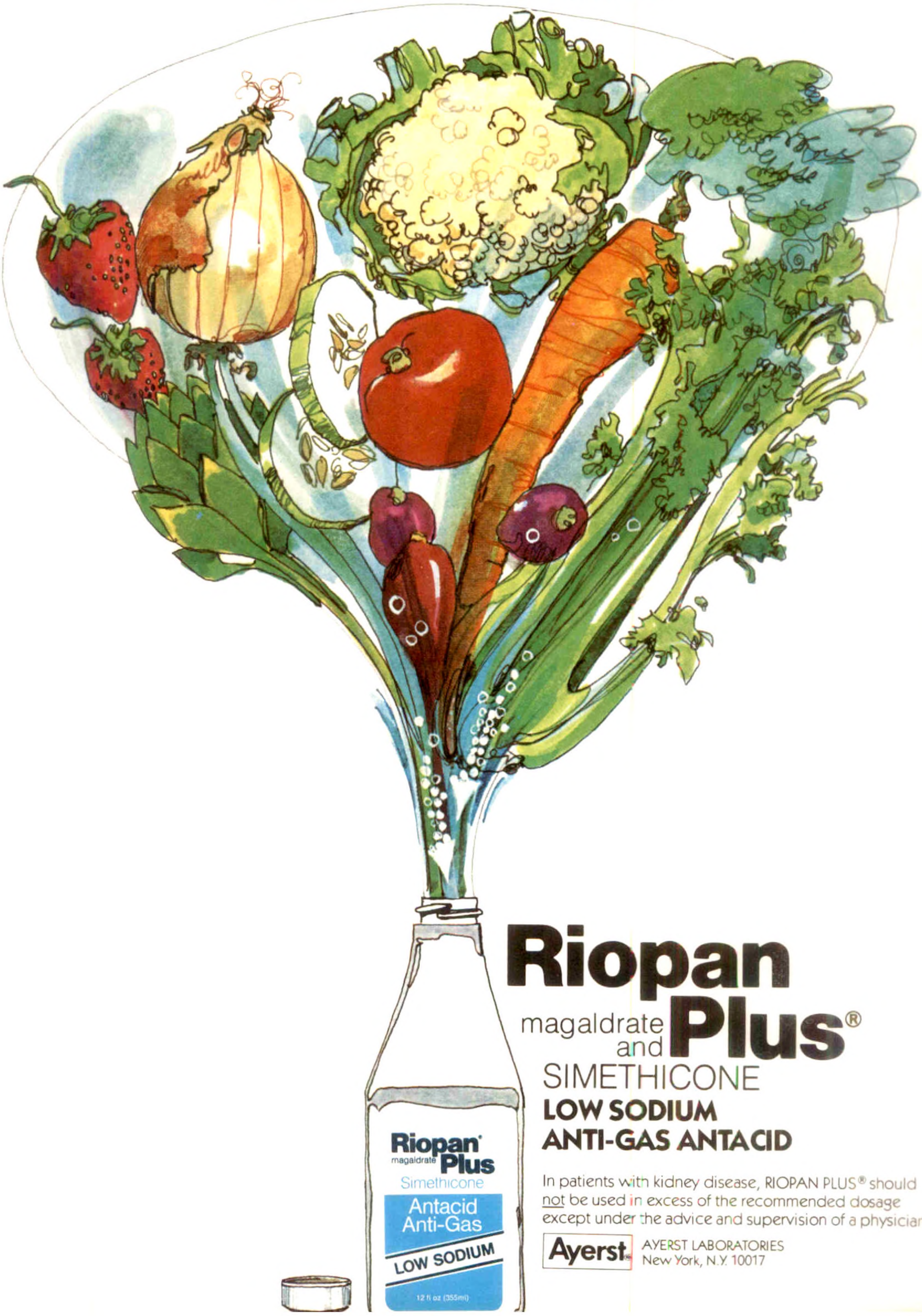

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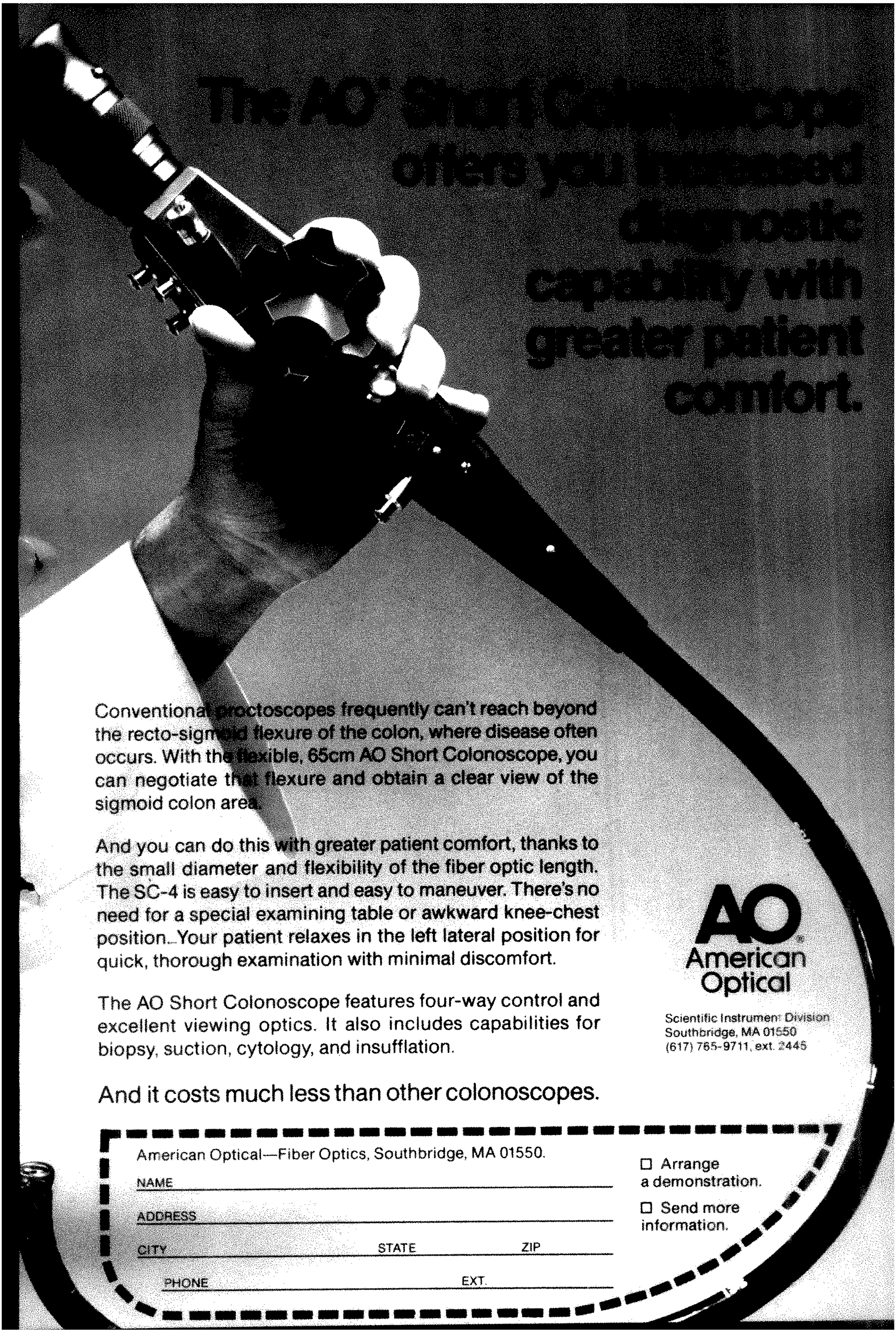

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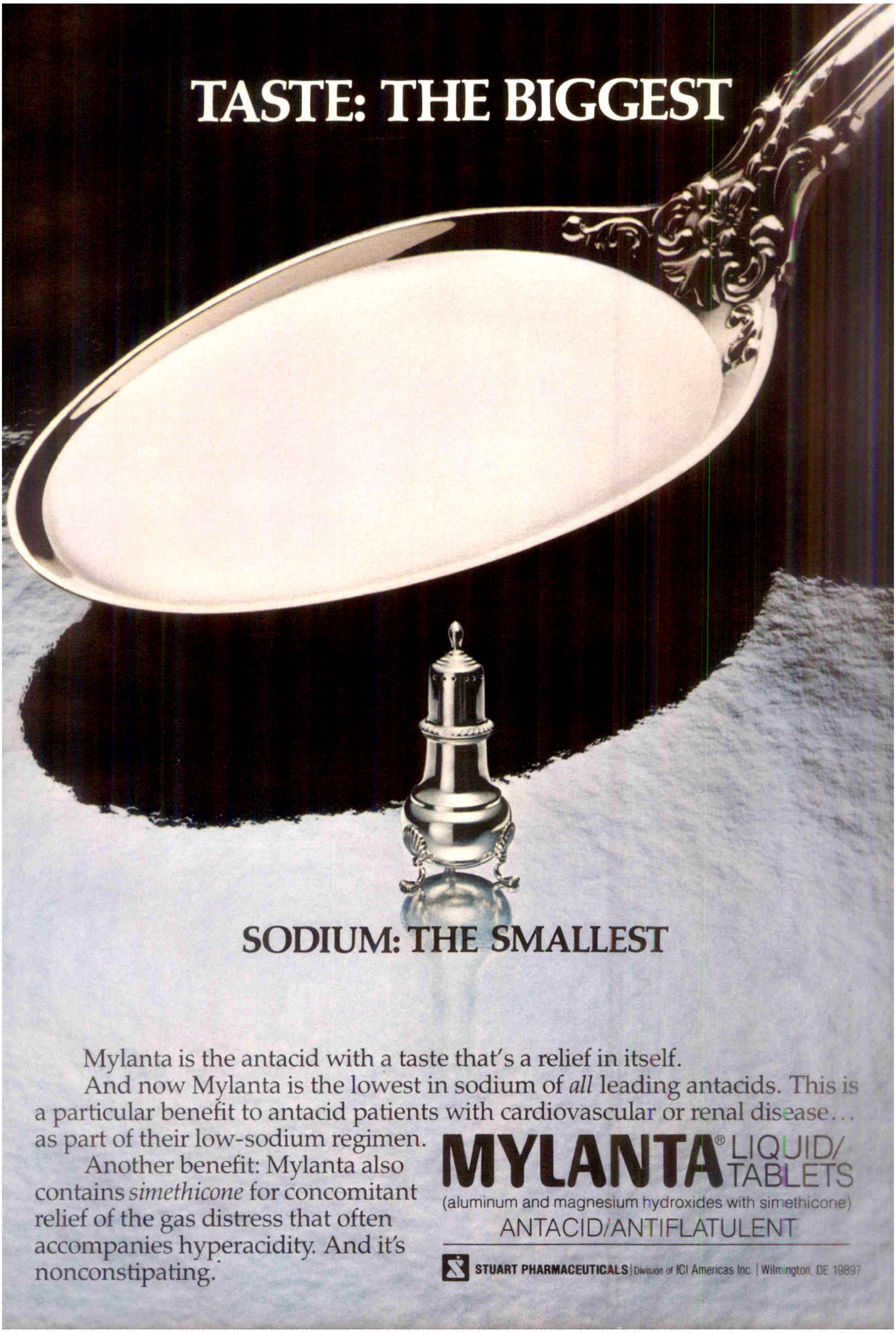

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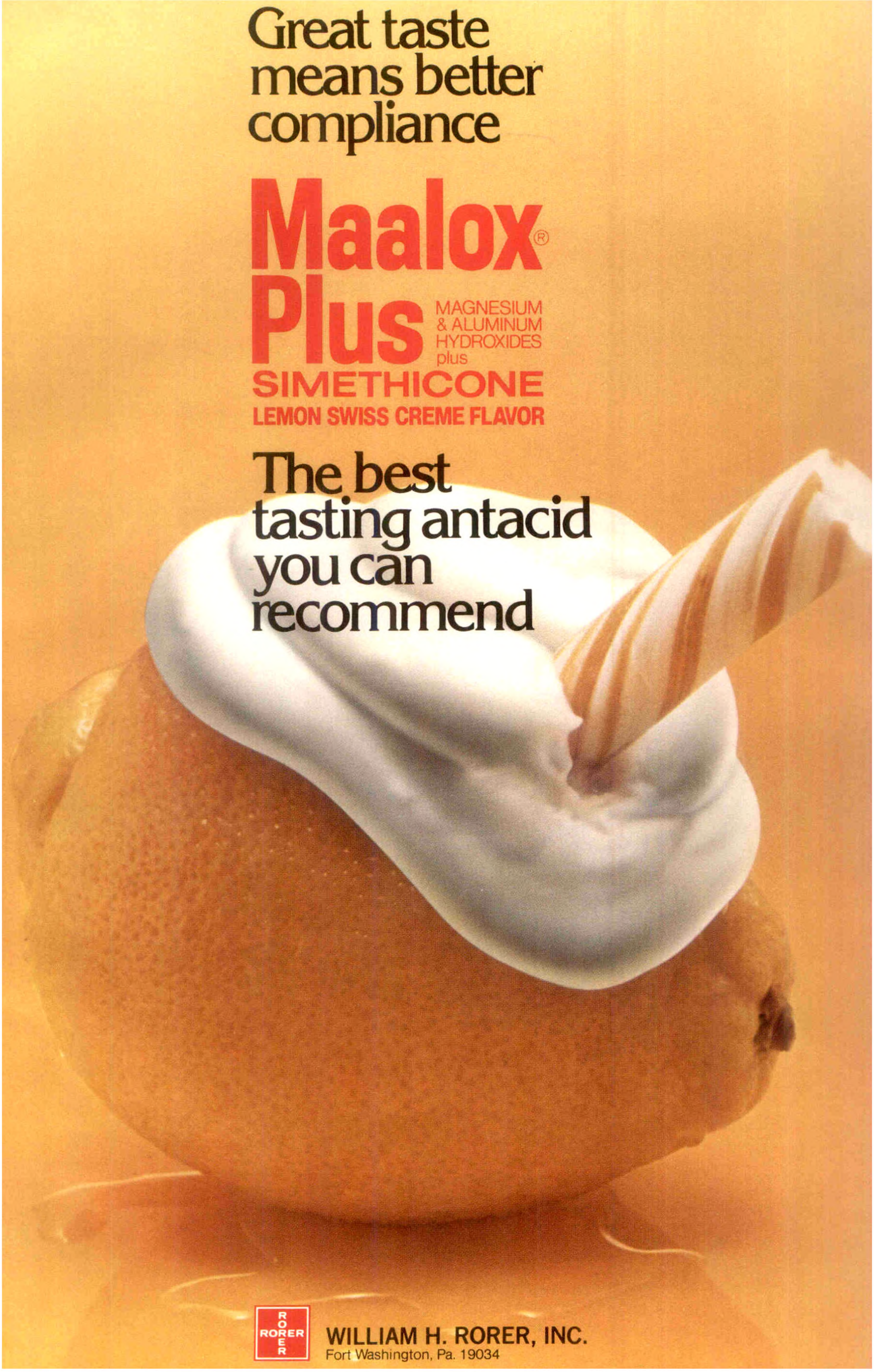

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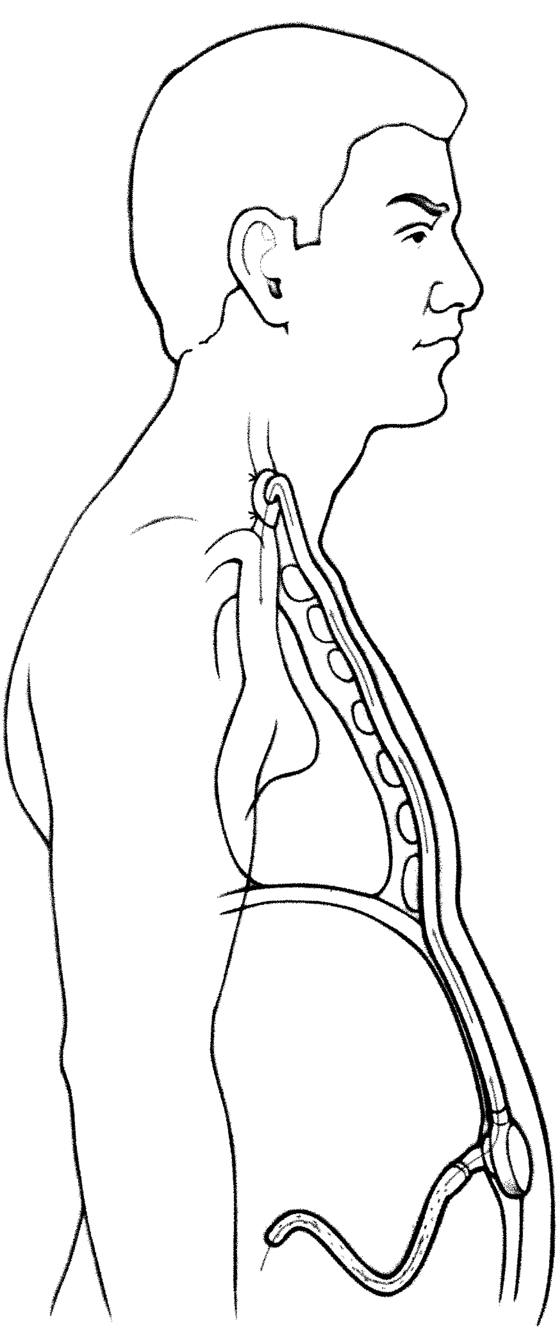
**WILLIAM H. RORER, INC.**
Fort Washington, Pa. 19034

# In refractory ascites the LEVEEN Peritoneo-Venous Shunt can achieve dramatic results



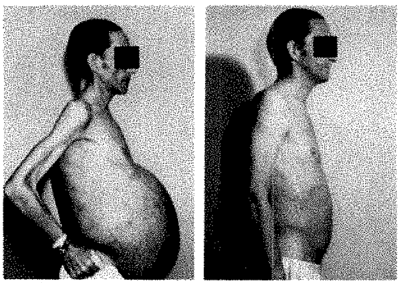
The LEVEEN Peritoneo-Venous Shunt can improve the prognosis of patients with ascites who become refractory to medical measures. It offers significant improvement in the control of ascites and reduces morbidity of such patients. The shunt can be used in ascites of varying origin.

## Removes and prevents fluid buildup

Implanted permanently in a simple surgical procedure, the LEVEEN Peritoneo-Venous Shunt returns peritoneal fluid to the superior vena cava through a pressure-sensitive extra-peritoneal valve. Through continuous reinfusion of the patient's own ascitic fluid, the shunt removes and prevents fluid buildup.

## Clinical experience

Postoperative improvement following insertion of the LEVEEN Peritoneo-Venous Shunt is often dramatic, particularly in the reduction of abdominal girth. Improvement is generally evidenced by: reduced weight, increased urine output, improved renal function, lowered BUN and creatinine levels, reduced aldosterone, elevated plasma protein (with a return of the albumin-globulin ratio toward normal), and greater patient comfort, mobility and ease of breathing. In many patients with marked wasting before surgery, appetite is improved and body mass is regained postoperatively.[1]



*Typical girth reduction in patient after shunt installation.*

**Dramatic relief of symptoms.** To date, the LEVEEN Peritoneo-Venous Shunt has been placed in more than 1,100 patients throughout the world. In one reported series of patients whose serum bilirubin was less than 10mg/100 ml, who had no evidence of severe encephalopathy, and no recent episode of upper gastrointestinal bleeding, 71% were alive 18 months later. At 18 months, these survivors had exceeded the survival rate expected for patients with refractory ascites treated with other accepted methods.[2]

For further information about the LEVEEN Peritoneo-Venous Shunt and its clinical experience, write to Ms. Peggy Harding, Becton, Dickinson and Company, Rutherford, N.J., 07070, or call this toll free number for answers to your technical questions: 800-631-0174. In New Jersey call 201-460-2251.

**The LEVEEN Peritoneo-Venous Shunt.**

**The reinfusion shunt controls ascites through continuous reinfusion of the patient's own ascitic fluid.**

*The LEVEEN Peritoneo-Venous Shunt is an in vivo device containing a unique, one-way valve which permits the unidirectional flow of ascitic fluid from the abdomen to the vascular system whenever the intraperitoneal pressure exceeds the central venous pressure by 3 cm. of water.*

B·D **BECTON-DICKINSON**
Division of Becton, Dickinson and Company
Rutherford, N.J. 07070

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**Indications For Use:**

The LEVEEN Peritoneo-Venous Shunt may be indicated when the patient does not respond promptly to intensive medical management.

The shunt is designed to eliminate the accumulation of ascitic fluid. Shunt placement should be considered for treatment of ascites complicating the following conditions:

1. Cirrhosis
2. Budd-Chiari Syndrome
3. Chylous Ascites
4. Nephrogenic Ascites
5. Biliary Atresia
6. Amyloidosis
7. Cryptogenic Ascites

**Contraindications For Use:**

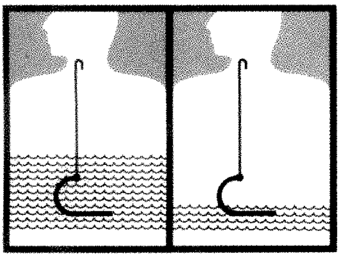
In certain patients, the LEVEEN Peritoneo-Venous Shunt will not be effective, or may be contraindicated because of secondary complications that outweigh its benefits. These conditions are:

1. **Peritonitis.** This should always be suspected when the peritoneal fluid is turbid. Peritonitis can occur without the usual signs and symptoms in patients with ascites.
2. **Esophageal Varices with a Recent History of Bleeding.** If ascites and variceal bleeding are present concurrently, treating the varices first may be indicated.
3. **Renal Failure.** The shunt will not reverse the renal damage in patients with acute tubular necrosis or other types of primary renal failure. A low urine sodium concentration may be the best indication that the tubules are functional and may respond to a shunt.
4. **Bilirubin level above 10 mg/dl.**

**Cautions:**

1. **Esophageal Varices without Recent Bleeding.** In patients whose varices have been treated surgically, the shunt may be effective.
2. **Neoplastic Ascites.** The LEVEEN Peritoneo-Venous Shunt has been used with success in patients with intractable ascites associated with primary or metastatic intra-abdominal neoplasms.[2] The use of the shunt in such patients requires weighing the shunt's potential benefits against the possible hazard of generalized dissemination of neoplastic cells which are commonly present in the ascitic fluid of these patients.
3. **Associated Cardiac Disease.** Cardiac patients may be sensitive to increased blood volume due to sudden recirculation of large quantities of ascitic fluid. Removal of accumulated ascitic fluid from the abdomen at the time of shunt placement may be indicated in such patients.

1. LeVeen, H. H., Wapnick, S., et al: Further experience with Peritoneo-Venous Shunt for Ascites. Annals of Surgery, 184:574-581, 1976.
2. Wapnick, S., Grosberg, S., et al: LeVeen Continuous Peritoneal-Jugular Shunt. JAMA, 237:131-133, 1977.

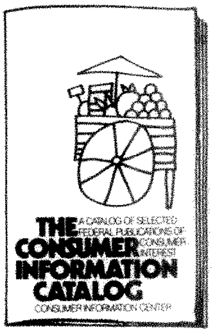


# "I CAN HELP CHANGE YOUR LIFE. BUT I CAN'T HELP CHANGE YOUR SPARK PLUGS."

If you want to find inner peace, come see me. But ask me how to fix a car? You got me. For questions of that nature, you must seek knowledge somewhere else.

A good place would be the Consumer Information Catalog. It is put out by the Federal Government and lists over 200 consumer booklets that one can send away for. Most are free. And they can help you in many areas that I cannot. From raising tomatoes to lowering your fuel costs.

So send for the free catalog. Write: Consumer Information Center, Dept. A, Pueblo, Colorado 81009. That way you won't have to climb a mountain to gain knowledge. You can merely go to your mailbox.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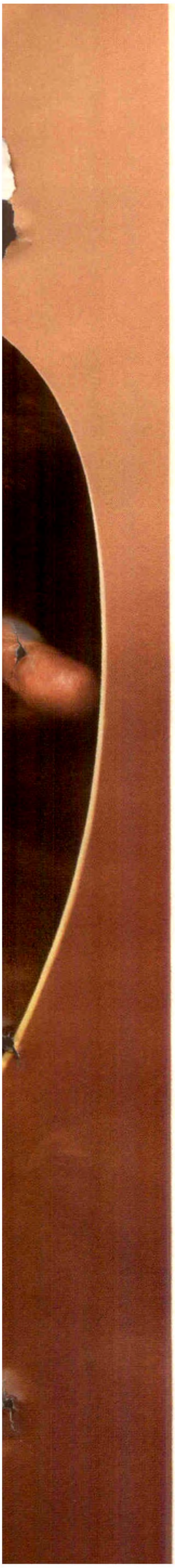
Some anxious ulcer patients manage to avoid every irritant...
CAFFEINE
FOODS HIGH IN ACID
SMOKING



ROCHE

# ...except excessive anxiety

While his ulcer is still in its active stage, the patient is usually quite scrupulous about following "doctor's orders." For the time being, at least, he's willing to forego coffee, alcohol, spicy foods, even cigarettes. But there's one irritant that some of these anxious ulcer patients may be unable to avoid—or to handle. Excessive anxiety.

For such patients, specific antianxiety medication is frequently indicated in addition to counseling and reassurance—that is where Valium (diazepam) comes in. Valium is a useful, highly dependable calming agent that works promptly to relax the patient and relieve his psychic tension and anxiety.

The characteristic response it produces is one that you know, want and trust.

Valium (diazepam) can particularly benefit the ulcer patient whose psychic tension increases at bedtime. The addition of an *h.s.* dose of Valium to a *b.i.d.* or *t.i.d.* regimen can reduce "nighttime" anxiety and thus may encourage sleep. At recommended dosages, Valium is usually well tolerated. Although drowsiness, ataxia and fatigue are sometimes encountered, these and more serious side effects are rarely a problem.

# VALIUM® (diazepam) Ⓘⓥ

2-mg, 5-mg, 10-mg scored tablets

## can relieve the ulcer patient's psychic tension and anxiety

**Before prescribing, please see following page for a summary of product information.**

VALIUM®
(diazepam)

**Before prescribing, please consult complete product information, a summary of which follows:**

**Indications:** Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

**Contraindicated:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

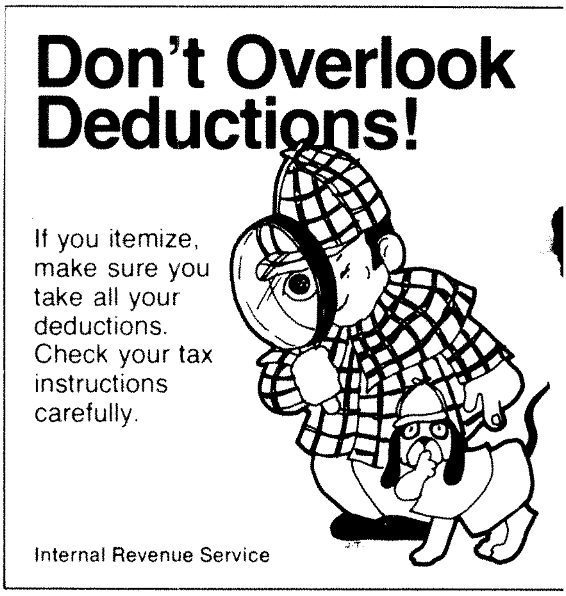
**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

**Dosage:** Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

**Supplied:** Valium Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

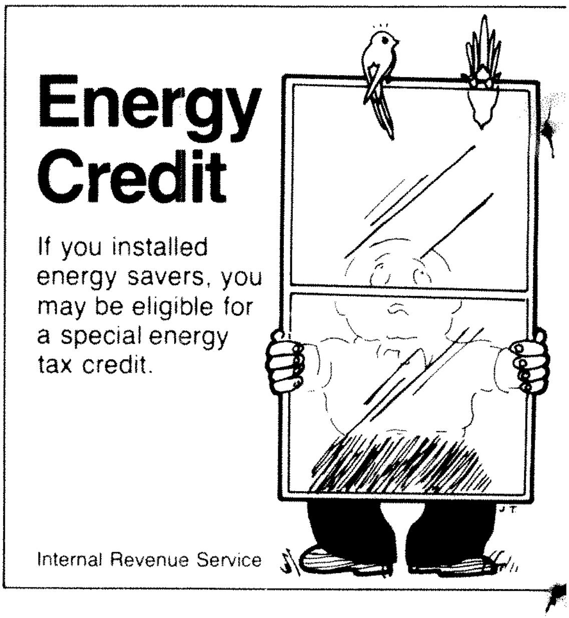
ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110



Don't Overlook Deductions!

If you itemize, make sure you take all your deductions. Check your tax instructions carefully.

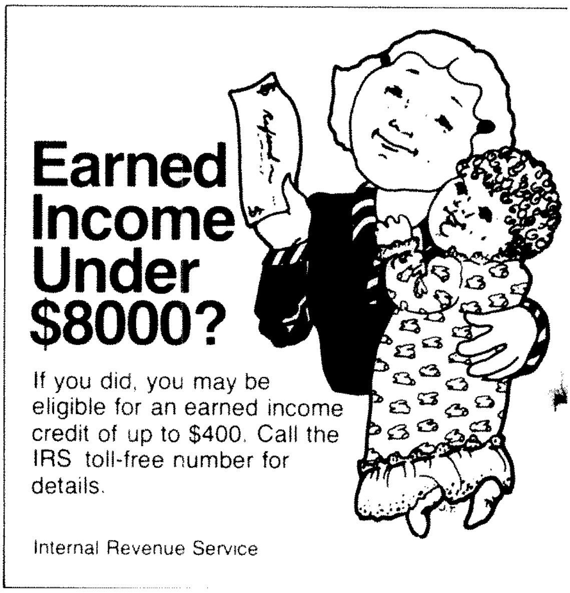
Internal Revenue Service



Energy Credit

If you installed energy savers, you may be eligible for a special energy tax credit.

Internal Revenue Service



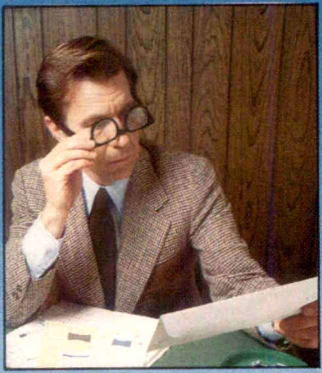
Earned Income Under $8000?

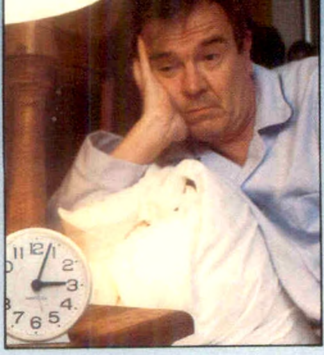
If you did, you may be eligible for an earned income credit of up to $400. Call the IRS toll-free number for details.

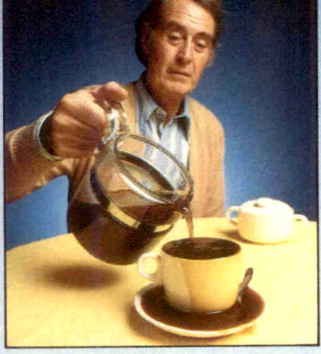
Internal Revenue Service

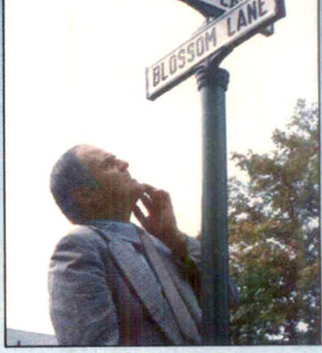
# Which of these cirrhotic patients has portal-systemic encephalopathy (PSE)?

***(Also called Hepatic Encephalopathy, Hepatic Coma.)***









(Please turn page for answer.)

**Cephulac®**
**(lactulose) Syrup**
**Brief Summary**

**INDICATIONS:** For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

**CONTRAINDICATIONS:** Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

**WARNINGS:** *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

**PRECAUTIONS:** Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

**ADVERSE REACTIONS:** Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

**DOSAGE AND ADMINISTRATION:** The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

**Merrell**

MERRELL-NATIONAL LABORATORIES
Division of Richardson Merrell Inc.
Cincinnati, Ohio 45215 U.S.A.

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write to:

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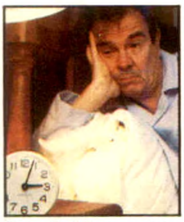
**Gastroenterology**
**299 Broadway**
**New York, N. Y. 10007**

# They all do!

**Case 1.** 53-year-old retired submariner with cirrhosis of uncertain etiology and portacaval shunt

**Case 2.** 57-year-old widow with primary biliary cirrhosis



**Case 3.** 50-year-old male with alcoholic cirrhosis

**Case 4.** 43-year-old salesman with clinically stable Laennec's cirrhosis

**Case 5.** 55-year-old male with histologically proven cirrhosis

BLOSSOM LANE

**Case 6.** 50-year-old male with Laennec's cirrhosis and portacaval shunt

Professional models were used to ensure patient privacy.

---

## Suspect portal-systemic encephalopathy (PSE) in every patient with cirrhosis

### Common early symptoms of PSE are:

irritability, euphoria, lack of concern for others, inappropriate behavior, faraway look, inversion of sleep pattern.

### Results of recent investigations of PSE:

- Two-thirds of cirrhotic patients with portal hypertension without clinical evidence of PSE revealed impairment of cerebral function on psychometric testing. This dysfunction was in the same range as in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

These inapparent and early stages can last for hours, days, weeks, months or even years. Untreated, they lead to COMA. You can't depend on routine observation to detect PSE.

- Test every cirrhotic for PSE.
- Treat every PSE, regardless of stage.
- Remember, the early stages are the most common; the coma stage is only the tip of the PSE iceberg.

Cephulac (lactulose) Syrup effectively reverses acute and chronic recurrent PSE in over 75% of episodes, without serious adverse reactions, when used as directed.

- lowers blood ammonia levels
- improves mental state
- lessens EEG abnormalities
- permits more normal dietary protein intake
- makes it easier to treat the patient

**References:**

**1.** Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
**2.** Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
**3.** Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: Detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

See adjacent page for prescribing information.

# Cephulac®
# (lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

## for the prevention and treatment of portal-systemic encephalopathy

***(Also called Hepatic Encephalopathy, Hepatic Coma.)***

# Which type of duodenal ulcer patient benefits most from 'Tagamet'?

☐ newly diagnosed patients

☐ duodenal ulcer repeaters

☐ refractory patients

☐ hospitalized patients

☑ all of the above

**Tagamet®**

brand of **cimetidine**

Tablets, 300 mg. Injection, 300 mg./2 ml.

Tagamet
cimetidine
Tablets

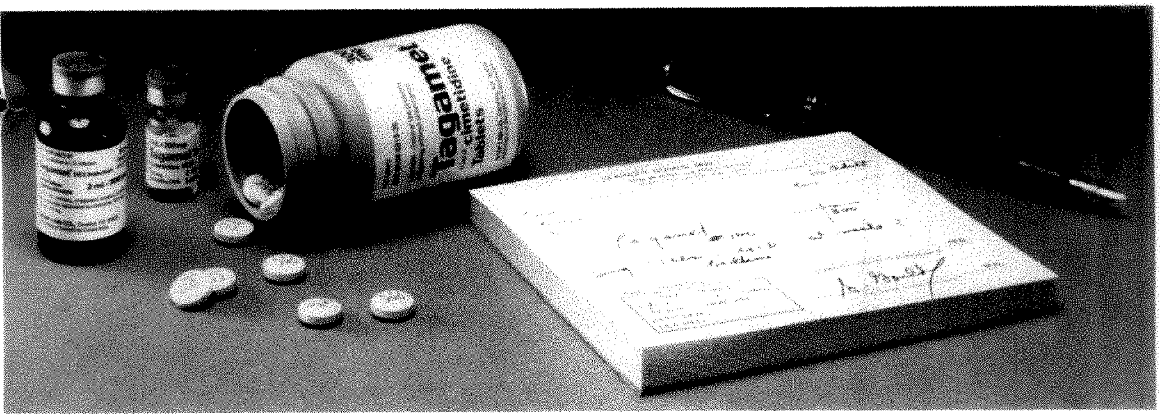
**SK&F LAB CO.**
a SmithKline company

# In all types of duodenal ulcer patients

# 'Tagamet'® brand of cimetidine

Tablets, 300 mg. Injection, 300 mg./2 ml.

## • Provides effective symptom relief, day and night
## • Promotes rapid ulcer healing
## • Is well tolerated



**Dosage in Duodenal Ulcer**

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

**Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.**

**Indications:** 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer, and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

**Contraindications:** There are no known contraindications to the use of 'Tagamet'.

**Precautions:** In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Potentiation of warfarin-type anticoagulants has been observed with concomitant 'Tagamet' administration. For this reason, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when these drugs are administered concomitantly.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

**Adverse Reactions:** Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

**How Supplied: Pale Green Tablets:** 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

**Injection:** 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials, in packages of 10.

Date of issuance Dec. 1978

**SK&F LAB CO.**, Carolina, P.R. 00630

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Papers presented before the 43rd Annual Convention of the American College of Gastroenterology.

These, in addition to other original articles, selected abstracts, editorials, book reviews, Radiology Corners, Endoscopy Corners, Pediatric Corners and "State of the Art" review articles.

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**Scriptformation**®

**Cortenema**®
disposable unit-dose
hydrocortisone retention enema

**COMPOSITION:** Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methylparaben, 0.18% as a preservative.
**INDICATIONS:** Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
**CONTRAINDICATIONS:** Systemic fungal infections; recent ileocolostomy.
**WARNINGS:** In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

*Usage in pregnancy:* Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

*Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response.* Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
**PRECAUTIONS:** Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
**ADVERSE REACTIONS:** Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:

*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
**DOSAGE AND ADMINISTRATION:** CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
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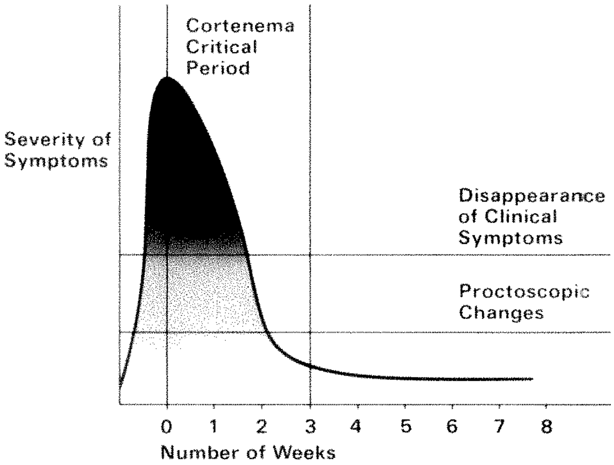

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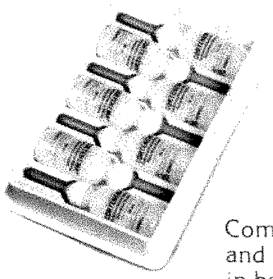

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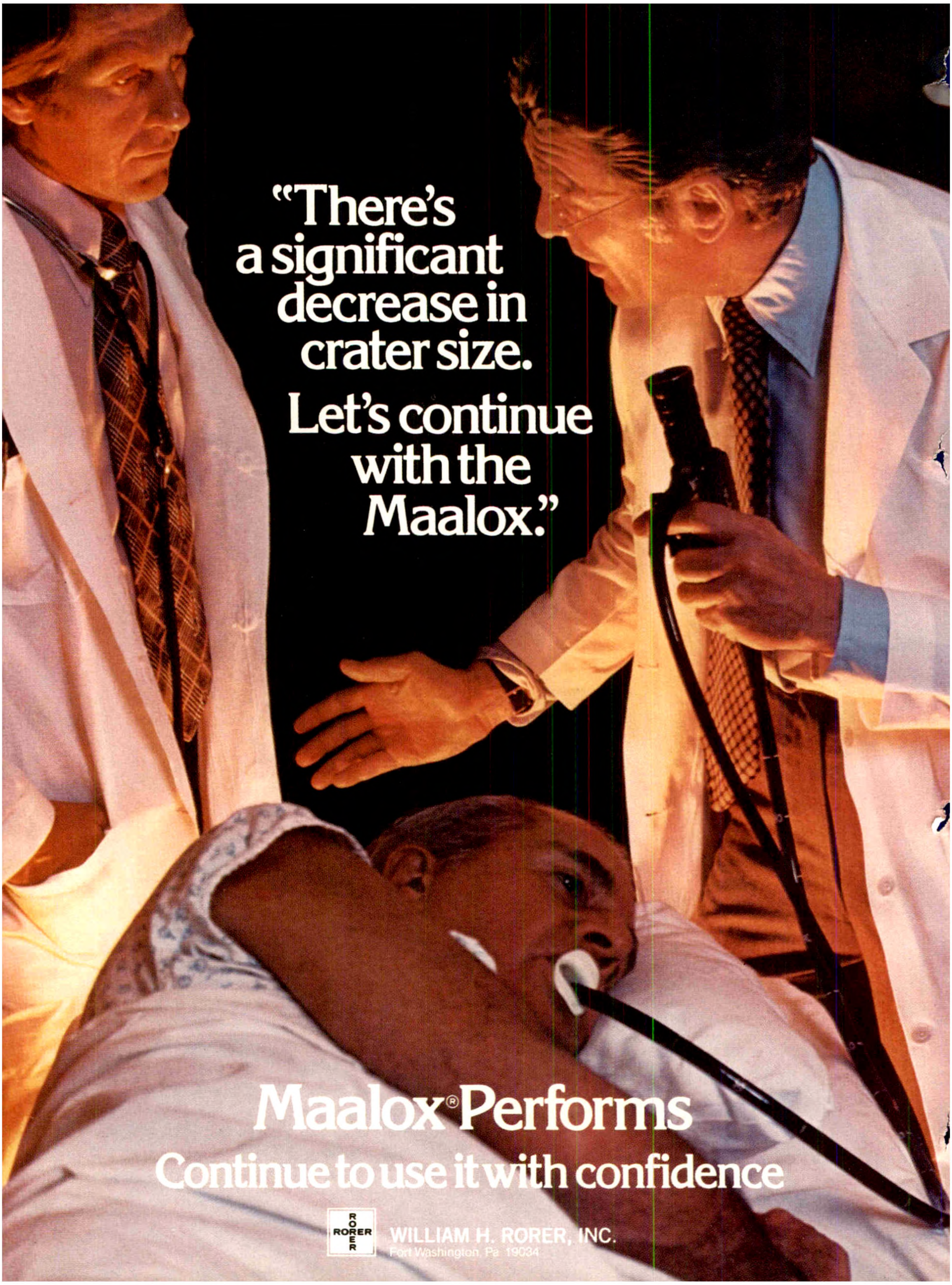

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# Effect of Endogenous Hyperprolactinemia on Human Lower Esophageal Sphincter Pressure

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The cause of gastroesophageal reflux occurring during pregnancy is not completely understood but may be related to changes in the hormonal environment specifically related to pregnancy. To evaluate the possible role of prolactin, one of the hormones elevated during pregnancy, we studied the effect of endogenously elevated serum prolactin concentrations, induced by I.V. thyrotropin-releasing hormone (TRH), on lower esophageal sphincter pressure (LESP) in normal subjects. Elevated prolactin concentrations ($P < 0.0001$), did not change LESP over a 60-minute period. Serum gastrin concentration did not change significantly at any time during the study. We conclude: 1. acute elevations of serum prolactin comparable to the concentrations that occur during pregnancy did not change LESP; 2. there is no evidence that the hypothalamic regulating factor TRH affects serum gastrin concentration in man.

Gastroesophageal reflux with symptomatic heartburn, a common complaint of pregnant women,[1-4] occurs in approximately two-thirds of all pregnancies.[5] A variety of mechanisms have been suggested to explain the pathogenesis of this heartburn. These mainly invoke anatomic factors such as increased abdominal pressure,[6] decreased resting lower esophageal sphincter pressure (LESP)[7, 8] and hiatus hernia.[9-12] Since heartburn is most common in the second and third trimesters and spontaneously subsides in most women after delivery, it has been hypothesized that changes in the hormonal environment specifically related to pregnancy may be responsible.[13-16]

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From the Sections of Gastroenterology and Endocrinology Medical and Research Services, Wadsworth Veterans Administration Hospital Center and the Department of Medicine, UCLA School of Medicine.

Supported by the Veterans Administration Research Service.

LESP is reduced during pregnancy, reaches a nadir in the third trimester and returns to normal in the postpartum period.[14] Increase of plasma progesterone, alone or in combination with estrogens, occurs during pregnancy and may explain the reduction in LESP.[14] In addition to the increased progesterone and estrogen levels during pregnancy, serum prolactin concentration is elevated.[17] This hormone, hence, may also play some role in the changes occurring in LESP. The purpose of the present study was to evaluate this possibility by investigating the effect of endogenous hyperprolactinemia, induced by thyrotropin releasing hormone (TRH), on LESP in normal subjects.

## METHODS

This study was approved by the Wadsworth Veterans Administration Hospital Human Research Committee. Informed consent was obtained from each subject. Six euthyroid normal male subjects without history of esophageal disease and with normal upper gastrointestinal roentgenograms, were studied. They ranged in age from 35-65 years. No subject received medications known to increase serum prolactin concentrations. Following an overnight fast, a standard 4-lumen polyvinyl tube assembly for measuring intraluminal esophageal pressures was swallowed by each subject. Each tube had a 1.2 mm. lateral orifice. Each lumen was perfused with water at 0.8 ml./min. The three distal orifices were 1.5 cm. apart, the remaining orifice was 5 cm. proximal to the second orifice. Pressures were transmitted to transducers (Statham Instruments, Hato Rey, PR) which in turn were connected to an amplifying and recording system (Electronics for Medicine, Fullerton, CA). Patients were supine throughout the study. A belt pneumograph about the neck recorded swallows. LESP was measured by a rapid pull-through technic.[18, 19] The three distal orifices were passed into the stomach and, with the subjects cooperating by not swallowing and by holding their breath at the end of a normal expiration, the three distal orifices were pulled through the LES into the esophagus over 15 seconds. LESP for each pull-through was calculated as the average of the highest pressures recorded by each of the three sensors. Pressures were recorded in mm. Hg. above mean fundic pressure. The basal LESP was determined by the mean of four pull-throughs over 15 minutes. An indwelling 19-gauge needle was placed in an antecubital vein and baseline samples of blood were drawn. On separate days and in a double-blind random fashion, subjects received 500 $\mu$g. of thyrotropin releasing hormone (TRH) or 1 cc. 0.15 NaCl as an intravenous injection over 30 seconds. LESP was then monitored for 60 minutes after this injection by a single pull-through performed at 10-minute intervals. The manometric recordings were read without knowledge of the drug administered.

Venous blood samples for determination of serum prolactin, thyrotropin (TSH), and gastrin concentrations were obtained basally (at -15 and 0 minutes) and then at 15-minute intervals for 60 minutes following I.V. TRH or placebo. After clotting at room temperature, serum was obtained by centrifugation and stored at -20° C until assayed. Serum prolactin was measured by minor modification of the homologous radioimmunoassay described by Sinha, et al[20] using reagents provided by the National Pituitary Agency, NIAMDD. In this assay, the mean basal serum prolactin was 5.7 ± 2.2 (SEM) ng./ml. in a large group of normal male controls. Serum TSH was measured by the sensitive double antibody radioimmunoassay described by Pekary, et al.[21] The mean basal TSH in normal individuals was 1.5 ± 1.0 (SD) $\mu$U./ml. for

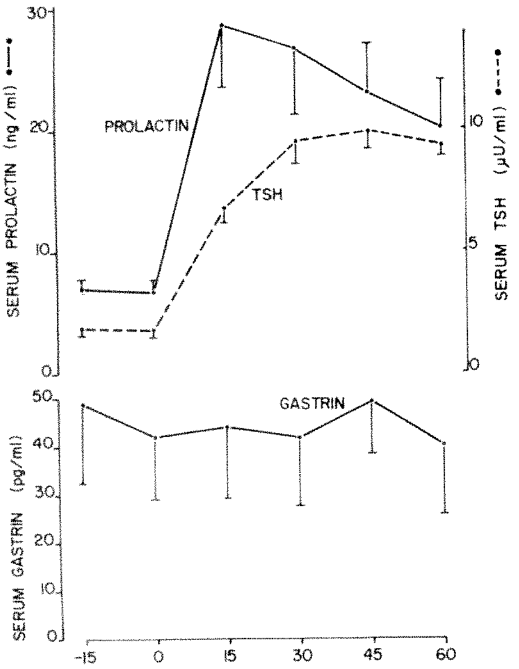

Fig. 1–Mean (± SEM) serum prolactin, TSH and gastrin concentrations in six normal men measured basally and at 15-minute intervals for 60 minutes following I.V. administration of 500 $\mu$g. TRH.

this assay. Serum gastrin concentrations were measured by radioimmunoassay.[22, 23] Synthetic human gastrin 1 was used as the standard. Normal serum gastrin for the assay was < 100 pg./ml. and the median gastrin value for normal subjects was 40 pg./ml. For each hormone, all serum samples were assayed in duplicate and all determinations for the study done in one assay.

Statistical comparisons were made using Student's "t"-test for paired data and one-way analysis of variance.[24]

## Results

After the I.V. administration of 500 $\mu$g. of TRH, serum prolactin concentration increased from a basal level of 7 ± 1 ng./ml. (Mean ± SEM) to a peak of 29 ± 5 at 15 minutes ($P < 0.0001$) and remained significantly elevated through 60 minutes (20 ± 4 ng./ml.) ($P < 0.001$) (Fig. 1). Serum gastrin concentration did not change significantly from the basal level during the study (Fig. 1). Serum TSH concentration increased from basal levels by 15 minutes ($P < 0.0001$) and remained elevated through 60 minutes (Fig. 1). No significant changes in the three hormone concentrations occurred after the placebo.

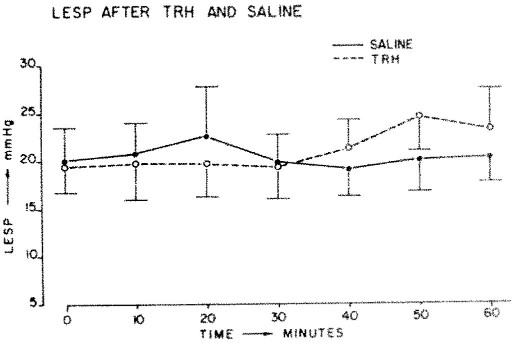

Fig. 2–Mean (± SEM) LESP in six normal men measured basally and at 10-minute intervals following I.V. administration of 500 $\mu$g. TRH and 0.15 M NaCl.

Basal LESP in six subjects on the TRH study day, 19.3 ± 2.6 mm. Hg. (mean ± SEM), was similar to the saline study day (19.9 ± 3.5 mm. Hg.). There were no significant differences in LESP response between the TRH and placebo days when absolute sphincter pressure was measured for 60 minutes after each injection and compared at 10 minute intervals (Fig. 2). The peak LESP attained after TRH was not significantly different from the peak LESP after the placebo. The changes from basal LESP ($\Delta$LESP) at each time interval for the two days were similar. The mean $\Delta$LESP for the six pull-throughs during the study period for each subject after TRH was also similar to placebo as determined by analysis of variance. No side-effects were noted by the subjects during the study.

## COMMENT

The prolactin concentration in pregnancy has been reported to increase after the 14th week of gestation, remaining elevated (approximately 4-fold) during the remainder of pregnancy.[17] Prolactin, in similar concentrations, potentiated the responses of rat vascular smooth muscle to noradrenalin[25] and increased arterial blood pressure in rabbits.[26] In our studies, prolactin concentrations were elevated in normal subjects to serum levels comparable to those occurring in pregnancy without affecting resting LESP.

It has been suggested that the increase of plasma progesterone, alone or in combination with estrogens, may explain the reduction in LESP occurring mainly in the second and third trimesters of pregnancy.[14] Recently, the progestational agent, dimithisterone, alone or in combination with an estrogen, was found to reduce LESP in nonpregnant female subjects.[16] During the first 20 weeks of pregnancy, the LES response to stimulating agents is diminished[15] and *in vitro* studies have found that the LES muscle response to stimulation is reduced in the presence of 17-beta-estradiol and/or progesterone.[15] The reduction of LESP during pregnancy, acting in concert with other factors, may conceivably allow gastroesophageal reflux to occur with the development of symptomatic heartburn. Among the other factors may be: the degree of weight gain; the type of foods ingested;[27, 28] prepregnancy LESP and state of sphincter competence and individual LES sensitivity to circulating levels of other hormones which contribute to the hormonal milieu of pregnancy. The need for interaction of factors may explain why all pregnant women do not experience symptomatic heartburn.

The findings here reported suggest that the hyperprolactinemia, which contributes to the hormonal milieu of pregnancy, does not seem to play a role in the reduced LESP reported to accompany pregnancy.[14] The possibility that hyperprolactinemia inhibits the LESP response to gastrin and other stimulants, however, was not studied. It is also possible that the LES in pregnant women may respond to hyperprolactinemia in a different way from the adult males observed in the present study.

In normal subjects, TRH, a tripeptide normally synthesized and secreted by the hypothalamus, releases thyrotropin (TSH) and prolactin but not growth hormone, luteinizing hormone, ACTH,[29] or insulin[30] and no systemic or organ-specific effects have been found.[30] To our knowledge, the gastrin response to I.V. TRH has not been studied. TRH, in the present study, did not change serum gastrin concentrations, suggesting that the hypothalamic regulating factor, TRH, has no role in gastrin release in man.

## ACKNOWLEDGMENTS

The authors thank Dr. J. M. Hershman for encouragement, Nancy Meyer and Jung Park for performing the prolactin and TSH radioimmunoassays, Dr. J. H. Walsh and Helen Wong (Grant AM17294) for performing the gastrin radioimmunoassay, Ms. Anna Husz and Frances Taylor for secretarial assistance and the Wadsworth Veterans Administration Hospital and the Gastrointestinal Various Donors fund for financial support.

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# Gallium-67-citrate Scanning in Tuberculous Peritonitis

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A 32-year old black, alcoholic male was noted to have an abnormal Gallium-67-citrate scan during a work-up for persistent fever. Surgical biopsies revealed findings of the dry form of tuberculous peritonitis. The literature concerning Gallium-67-citrate scanning was reviewed and its usefulness in inflammatory disease states (including two reports of positive scans in tuberculous peritonitis) was demonstrated. In addition, we have considered the possible mechanisms of Gallium-67-citrate uptake by inflammatory cells and its probable relationship to the granulomas associated with tuberculous peritonitis.

We conclude that Gallium-67-citrate scanning is an important diagnostic procedure in the evaluation of a fever of unknown origin. Moreover, it may significantly shorten the diagnostic work-up of those cases of tuberculous peritonitis.

## INTRODUCTION

Tuberculous peritonitis, which may present in the absence of clinically apparent tuberculosis elsewhere, is an insidious, often cryptic but potentially curable disease.[1] This illness is a reactivation form of tuberculosis which results from the spread of tubercle bacilli to the peritoneum from such abdominal foci as the mesenteric lymph nodes or from extraabdominal sources. Pathologically, the disease process is the same as that in other parts of the body and the diagnosis most commonly is based on such histologic findings as caseating granuloma obtained by percutaneous needle biopsy of the peritoneum,[2] or by exploratory laparotomy.[1]

Tuberculous peritonitis is classified into two forms: the ascitic or wet and the adhesive or dry forms.[3] Initially, the presence of ascites usually leads one to consider the diagnosis of tuberculous peritonitis. The absence of ascites (the dry form), however, may lead one to overlook the correct diagnosis. Arriving at an early diagnosis in such cases of tuberculous peritonitis is of utmost importance.

Although Edwards and Hayes[4] initially demonstrated the usefulness of Gallium-67-citrate scintigraphy in the diagnosis of malignancies, Gallium-67 scanning has been used to detect areas of inflammation.[5-8] This report confirms earlier observations[9, 10] that Gallium-67-citrate scanning can be used as an important adjunct in establishing the diagnosis of tuberculous peritonitis early in the hospital course.

## CASE REPORT

W. S., a 32-year old black male, was admitted to Bellevue Hospital on 22 Febru-

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From the Departments of Medicine (Gastroenterology) and Radiology, Bellevue Hospital Medical Center.

ary 1977 for evaluation of persistent diarrhea and fever.

The patient was in his usual state of health until six weeks prior to admission when he noted the onset of diarrhea. He experienced six to 10 watery bowel movements per day and several bouts of diarrhea during the night. The diarrhea was not related to food intake. The patient admitted to anorexia, nausea, fever and an 18 kg. weight loss during this period. He denied rectal bleeding, melena, abdominal pain, cough, night sweats or pruritus.

The patient had a past history of alcohol abuse, *delirium tremens* and pneumonia. He was receiving no medications.

Physical examination revealed a cachectic appearing black male in no acute distress. His temperature was 39° C, respiratory rate 20/min. and his blood pressure was 110/60. All the abnormal findings were confined to the abdomen which was described as slightly distended, tympanic, with diffuse tenderness and guarding. There was no rebound tenderness and no evidence of ascites, masses or organomegaly. The stool was trace guaiac positive. Peritinent laboratory data included a hematocrit of 36%, white count of 14,800 with 78% segmented neutrophils, 14% bands and 7% lymphocytes. The sedimentation rate was 130 mm./hr.; BUN, 26 mg.; creatinine, 1.4 mg.; albumin, 2.3 gm.; globulins, 4.3 gm. The liver tests were normal except for an elevated LDH of 318 I.U. (normal 70-175). Urinalysis and chest x-ray were negative.

*Hospital course:*—The patient remained febrile during his hospital course with daily temperature spikes as high as 39.3° C. A PPD was negative. The patient was found to be anergic. Stool and blood cultures were negative. Stool was negative for ova and parasites. X-ray studies, which included barium enema and intravenous pyelogram and a liver scan, were normal. An upper gastrointestinal series revealed thickened gastric folds with dilation of the small bowel and increased secretions. An upper gastrointestinal endoscopy revealed thickened gastric and duodenal folds. A small bowel biopsy showed moderate infiltration with plasma cells and eosinophils. There was no evidence of lymphoma or sprue.

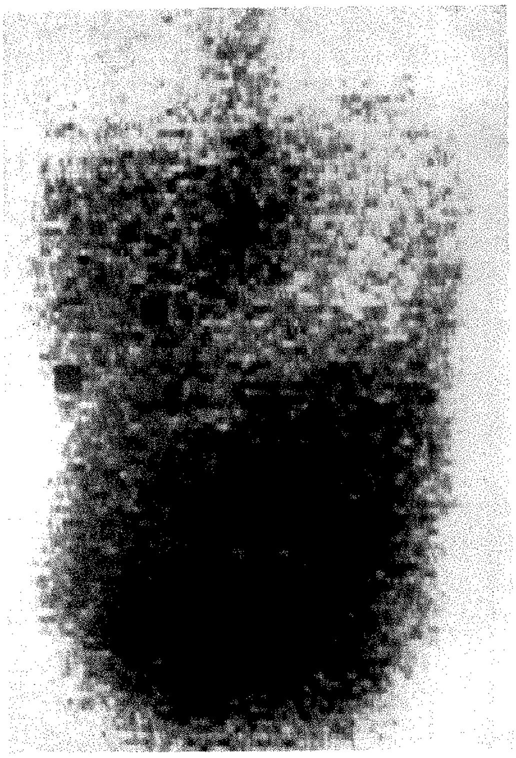

Fig. 1—Scan done 48 hours after intravenous dose of Gallium-67-citrate showing marked homogeneous uptake of the radionuclide throughout the peritoneal cavity.

A Gallium-67-citrate scan was performed to rule out the possibility that a lymphoproliferative disorder or an infectious focus might be the etiology for the fever.

A 5-mCi intravenous dose of Gallium-67-citrate was administered 48 hours prior to scanning. The bowel was cleansed rigorously in order to rid the abdomen of normal colonic radiogallium activity. Images were obtained on a Picker Magna Scanner 1000 (rectilinear) with 4:1 minification. The spectrometer was set to utilize 184- and 296-keV photopeaks.

The scan showed marked, homogeneous uptake of the radionuclide throughout the entire confines of the peritoneal cavity (Fig. 1). Diffuse inflammatory bowel disease, wide-spread abdominal carcinomatosis, malignant lymphomatosis and peritonitis could be expected to yield this pattern.

In view of the inability to make a definitive diagnosis despite the abnormal Gallium-67-citrate scan, a laparotomy was performed. Exploratory laparotomy revealed numerous necrotic lesions seeding the anterior abdominal wall. White nodules were noted throughout the peritoneum and the entire abdominal cavity was encased in a sheath studded with white nodules about 1 cm. in diameter. Microscopic examination of the biopsy specimen revealed caseating granulomas which were positive for acid fast bacilli. The patient was started on treatment with Isoniasid and Rifampin with marked clinical improvement.

## COMMENT

Gallium-67 is a carrier free metal that is produced in the cyclotron and has a half life of 78 hours. It decays by electron capture and emits four major gamma rays that can be used for scanning. It is usually administered as an intravenous injection of Gallium-67-citrate formed by adding sodium citrate to the radionuclide. Localization of the Gallium-67 can be detected with rectilinear scanners, and scintillation camera.

Initial reports by Edwards and Hayes[4] demonstrated that Gallium could be used as a radioisotope scanning agent for the detection of a variety of human malignancies. This observation provided the impetus for the investigation of the radionuclide as a tumor-scanning agent by others.

Gallium scintigraphy has also proven to be useful in detecting areas of inflammation. Sarcoidosis[11, 12] and a host of other inflammatory conditions[5-8] have been detected by Gallium-67-citrate scanning.

The mechanism of Gallium-67 accumulation in neoplastic and inflammatory foci has yet to be discovered. Several attempts at explaining the phenomenon, however, have been proposed. Acute inflammation is characterized by dilation of arterioles, increase in capillary blood flow and permeability and migration of polys, mononuclear cells and lymphocytes into affected tissues. Many workers have shown that Gallium-67 is bound to serum protein.[13, 14] These Gallium protein complexes may approach the site of inflammation associated with tumor or infection through various vascular channels. Once Gallium-67 is present in these sites in sufficient amounts, it may be taken up by the tumor cells or cells involved in the inflammatory response and its emission recorded by scanners.

Kinetics of Gallium-67 incorporation in inflammatory lesions was studied by Gilrud, et al.[15] Results of these studies showed that it is the presence of inflammatory cells rather than exudation of plasma protein that is responsible for the accumulation of Gallium.

Winchell[16] postulated that local lactic acidosis in metabolically active tumors caused increased disassociation of Gallium citrate with the formation of Gallium protein complexes which could be taken up by cells in and around the tumor. Evidence that Gallium-67-citrate can be taken up by tumor cells was first demonstrated by Hayes.[17] Tumor cells took up Gallium which accumulates primarily in the cytoplasm. This group later showed that most of the Gallium in these tumors was associated with electron dense cytoplasmic granules, bounded by a single membrane.[18] These granules were thought to be lysosomes. Hayes also demonstrated uptake of Gallium by macrophages and cells of the reticuloendothelium system in liver, spleen and bone marrow. Other lysosomal-rich cells, the neutrophils, also pick up Gallium.[19]

In cases of sarcoidosis, Gallium-67-citrate was shown to be taken up by the active granulomatous lesions[11, 12] presumably due to the presence of lysosome-rich histiocytes present in the granuloma. When these lesions responded to therapy a disappearance of the inflammatory cells with a concomitant drop in Gallium-67 concentration occurred. It appears that uptake of Gallium is largely dependent on the stage of the inflammatory activity.

Higasi, et al[20] also showed that active inflammation in their series of patients with tuberculosis resulted in positive scans, whereas inactive tuberculosis did not. This was confirmed by Ito, et al[21] who also showed a loss of Gallium scan positivity in cases of treated tuberculosis and in tumors subjected to radiation therapy and chemotherapy. Edwards and Hayes[22] observed this effect when cancer patients were treated with chemotherapy.

Tuberculous peritonitis is a form of tuberculosis which results from the spread of tubercle bacilli to the peritoneum from such abdominal foci as the mesenteric lymph nodes or from extraabdominal sources. The disease process is similar to that of other parts of the body. The accumulation of Gallium-67 in the abdominal cavity of our patient was most probably due to the presence of histiocytes and other inflammatory cells present in the granulomas characteristic of tuberculosis.

While we do not feel that Gallium scanning should replace peritoneal biopsy or laparotomy as the procedure of choice in establishing the diagnosis of tuberculous peritonitis, we do believe that judicious use of this diagnostic procedure may lead to an early diagnosis of tuberculous peritonitis in patients with a fever of unknown origin. This would thus spare the patient undue discomfort and delay in diagnosis and treatment.

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# Endoscopic, Histological and Ultrastructural Correlations in Chronic Gastritis

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Thirty-three patients presenting with dyspepsia were examined with the Olympus Fiber-gastroscope. An endoscopic diagnosis was made in each case and multiple gastric biopsies were obtained for histological and ultrastructural assessment. The endoscopic, histological and ultrastructural findings were compared with each other. Of 33 patients endoscoped, 29 were found to have endoscopic evidence of various types of gastritis and all of these latter had histological evidence of some form of gastritis. Histological confirmation of specific types of endoscopically diagnosed gastritis, however, was only found in 3/9 cases of chronic atrophic gastritis (CAG), 10/14 cases of chronic (superficial) gastritis (CG) and in none of six cases of acute gastritis (AG), indicating that endoscopic diagnosis of specific types of gastritis is relatively inaccurate. Endoscopic diagnosis should thus be restricted to presence or absence of gastritis, leaving the specific typing to histological assessment of the gastric biopsies. Multiple gastric biopsies should be obtained even though the gastric mucosa appears normal endoscopically, since histological evidence of gastritis was found in three out of four cases with endoscopically normal gastric mucosa.

Comparison of histological diagnosis with electron microscopy showed that generally there is good correlation between the severity of the histological changes and the ultrastructural grade of damage as defined in this study. It would appear that E.M. examination of the gastric biopsies will not significantly increase the diagnostic accuracy of light microscopy, although it has elucidated the various cellular changes which characterize chronic gastritis. The rough surface contours, the large gastric pit and the increasing number of surface microvilli, seen by scanning E.M., aid the grading of the disease process. Some of these changes are reflected in observations made by transmission E.M. where in addition the basal intercellular edema of the mucosal layer and the appearance of electron-dense mucosal lining cells are observed. The latter, which are the counterpart of "intestinal metaplasia", possess mucus granules which resemble those of gastric mucosal lining cells or intestinal goblet cells, or both.

## INTRODUCTION

Several previous reports on the endoscopic diagnosis of gastritis have given divergent results.[1-7] The value of endoscopy in the diagnosis of gastritis has thus been in doubt. Some of the difficulties in these pre-

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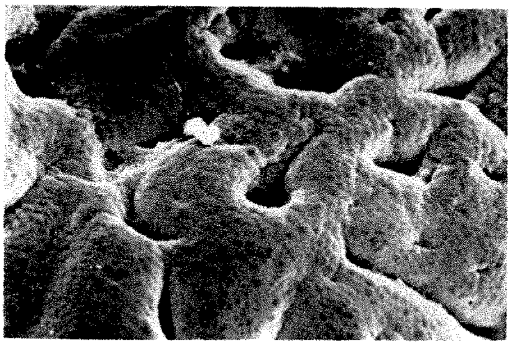

Fig. 1—Scanning electron micrograph of gastric mucosa showing only mild abnormalities. There is slight coarseness of the mucosal surface and some variation in the dimensions of the ostia (original magnification x900).

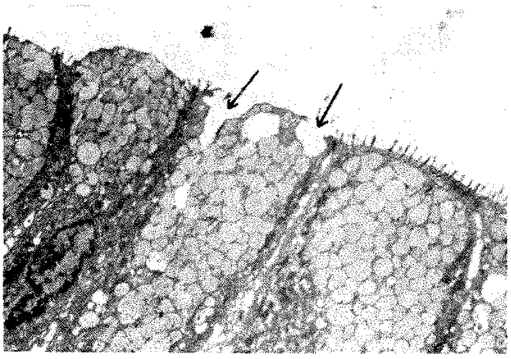

Fig. 3—Transmission electron micrograph of gastric mucosa showing mild abnormalities. The mucosal cells display deep surface indentations (arrows) (original magnification x7,000).

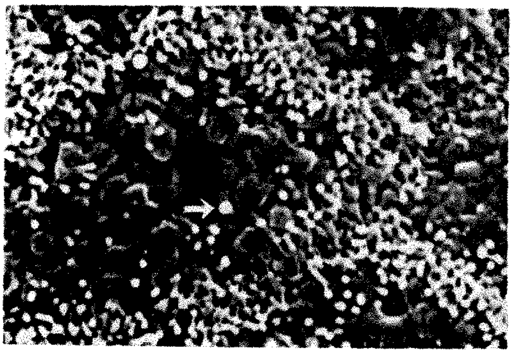

Fig. 2—Scanning electron micrograph of the surface of mucosal lining cells displaying only minor abnormalities. Many peripheral microvilli are present but globular projections are few (arrows) (original magnification x19,000).

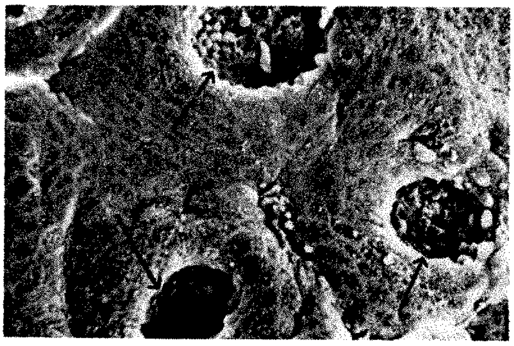

Fig. 4—Scanning electron micrograph of gastric mucosa with moderate abnormalities. The ostia of the gastric pits are dilated (arrows) and contain cell debris (original magnification x1,700).

vious studies have been attributed to the many disadvantages of the older semi-flexible gastroscope. With the introduction of the fiber-gastroscope many of these difficulties have been removed. Recent studies using the fiber-gastroscope have been reported to give a correct gastroscopic diagnosis in about 60-80% of cases.[8, 9] More recently, scanning and transmission electron microscopy have been used in the assessment of gastric biopsies obtained by the fiber-gastroscope.[10, 11] A variety of ultrastructural changes have been reported[10, 11] but the nature and significance of such changes remain to be clarified. The present study attempts to correlate endoscopic, histological and ultrastructural findings so that the accuracy of endoscopic diagnosis can be established and the value of scanning and transmission electron microscopy in the routine examination of gastric biopsies may be determined.

## PATIENTS AND METHOD

A total of 33 patients (18 males and 15 females), presenting with dyspeptic symptoms were subjected to endoscopic ex-

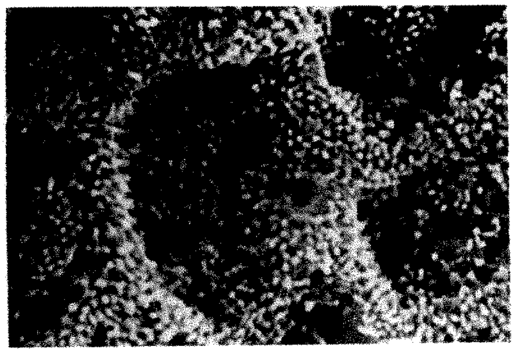

Fig. 5—Scanning electron micrograph of the surface of mucosal lining cells, displaying changes of moderate severity. The number of surface microvilli has increased and globular projections are more frequently seen (original magnification x17,200).

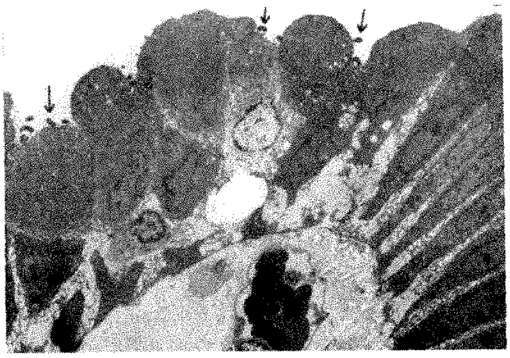

Fig. 6—Transmission electron miscrograph of moderately affected mucosa. The surface is irregular and bacteria (arrows) are present. The intercellular space between the basal portions of the lining cells is increased (original magnification x2,900).

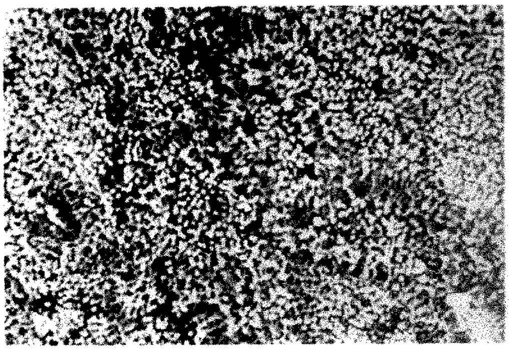

Fig. 7—Scanning electron micrograph of severely affected mucosa. Many microvilli and globular projections over the lumenal surface (original magnification x10,500).

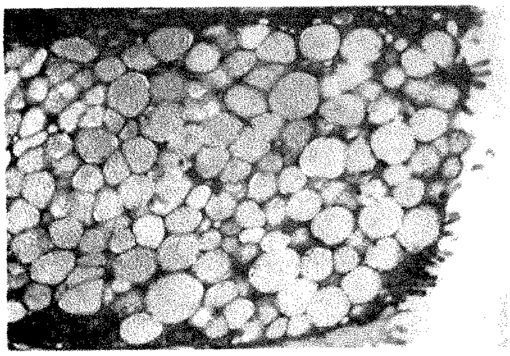

Fig. 8—Electron dense cell possessing granules with a fibrillar substructure (original magnification x16,200).

amination with the Olympus fiber-endoscope Models GIF 2, 3 and GFK. The patients' mean age was 53.2 years (ranging from 22-83 years). Each patient was fasted overnight and endoscoped the following morning under local anesthesia. An endoscopic diagnosis was made after thorough inspection of all parts of the stomach. Criteria used for the endoscopic diagnosis included the following: reddening of the mucosa, covering of mucosa with mucus or mucoid material, presence of acute inflammation and edema, presence of mucosal folds, visualization of blood vessels on the mucosal surface. The endoscopic diagnosis was classified according to the following: 1. acute gastritis, 2. chronic superficial gastritis and 3. chronic atrophic gastritis. Acute gastritis was diagnosed when there was severe reddening of the mucosa together with acute inflammation and edema and sometimes minute punctate hemorrhages, without presence of erosions. The term "erosive gastritis" was used when there was presence of acute erosions. Chronic (superfical) gasitritis was diagnosed when there was an increased diffuse reddening of the mucosa, mucus covering and presence of normal folds. The diagnosis of chronic atrophic gastritis was made when these changes of increased reddening and mucus covering were accompanied by a reduction

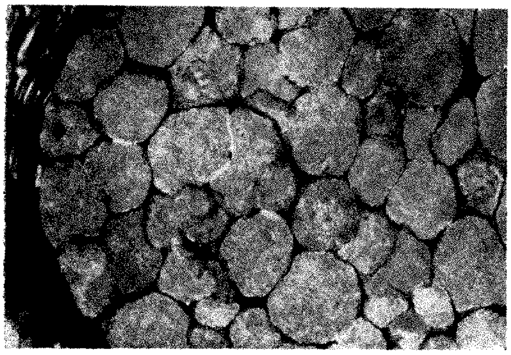

Fig. 9—Electron dense "goblet" cell containing granules with a fine punctate substructure (original magnification x23,000).

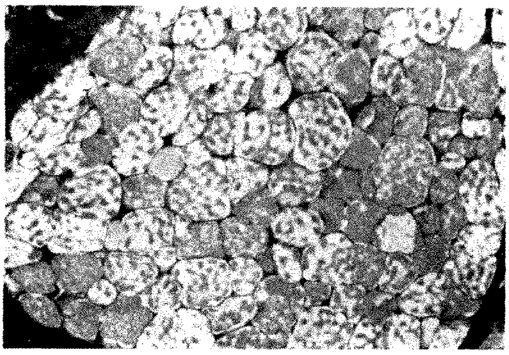

Fig. 10—Electron dense cell possessing some granules with a fibrillar substructure and others with finely punctate contents (original magnification x14,000).

in mucosal folding and an easily visible vascular network on the mucosal surface. After the endoscopic diagnosis was made, multiple biopsies were obtained from the antrum as well as from the corpus of the stomach. For each area, one or more biopsies were obtained and fixed in formal saline for histological examination, while another specimen was immediately put into 2.5% glutaraldehyde for electron microscopy (E.M.) The biopsies for histology and E.M. were obtained from adjacent areas of mucosa to reduce sampling error. Histological sections were carefully oriented, stained with hematoxylin and eosin and then assessed (L. R. M.) The diagnostic criteria for the histological assessment of the biopsy specimens are based essentially on those of Whitehead, et al.[12] Chronic (superficial) gastritis was diagnosed when there was inflammatory cell infiltration of the *lamina propria,* in both antral and corpus gastric biopsies. Chronic atrophic gastritis was diagnosed only when there was significant glandular atrophy affecting corpus gastric biopsies, in addition to the inflammatory changes for chronic (superficial) gastritis.

The specimens for electron microscopy were examined by scanning as well as transmission electron microscopy. Specimens for transmission electron microscopy were fixed for 16 hours in 2.5% glutaraldehyde in 0.1M cacodylate buffer (pH 7.4). They were then postfixed in 1% osmium tetroxide in 0.1M cacodylate buffer (pH 7.4) for 1 hour, dehydrated through ascending grades of ethanol and embedded in araldite. Semi-thin and ultrathin sections were cut on an LKB III ultramicrotome. The semithin sections were stained with 1% toluidine blue in 5% borax for light microscopic examination while the ultrathin sections were stained with lead hydroxide then examined on a Siemens Elmiskop 102 electron microscope at an accelerating voltage of 80 KV.

Specimens for scanning electron microscopy were fixed in glutaraldehyde as outlined above. Mucus was mechanically teased from the surface of the samples which were then placed on albuminized coverslips then dehydrated in graded solutions of ethanol. They were then dried in a Polaron critical point drying apparatus using amyl acetate and liquid $CO_2$ as the exchange solution. The samples were thin coated on a 600 A° layer of gold paladium or an Edwards vacuum evaporator and then viewed on the ETEC Scanning Electron Microscope using an accelerating voltage of 25 KV. The observations by electron microscopy were initially assessed without

TABLE I

Age, Sex, Endoscopic Diagnosis and E.M. Grading of Four Cases with Histologically Proven Chronic Atrophic Gastritis

| Age (yrs.) | Sex (M/F) | Endoscopic diagnosis | Gastric biopsy | |
|---|---|---|---|---|
| | | | Histological diagnosis | E.M. Grading |
| 80 | F | CAG | CAG + IM | III |
| 68 | F | CAG | CAG | III |
| 67 | M | AG | CAG | III |
| 70 | F | CAG | CAG | III |

AG = acute gastritis; CAG = chronic atrophic gastritis; IM = intestinal metaplasia.

prior knowledge of the histological or endoscopic diagnosis (JMP) and later compared with the other findings.

### Electron Microscopy

The ultrastructural features seen in the samples of gastric mucosa have been arbitrarily divided into three grades of increasing severity. The results of both scanning and transmission electron microscopy have been pooled and the two correlated. The characteristics of samples placed in Grade I show minimal deviation from the ultrastructure of the normal stomach while those of Grade III are the most abnormal. Apart from bacteria, no other microorganisms were detected.

*Grade I:*—Slight coarseness of the mucosal surface was detected by scanning electron microscopy as well as some variation in the size of the ostia of the gastric pits with many being somewhat dilated (Fig. 1). Many microvilli but few globular projections were seen on the more peripheral zone of the lumenal surface of the lining mucosal cells (Fig. 2) but the surface pitting of these cells was in the spectrum seen in normal stomachs by Fallah, et al.[11]

Transmission electron microscopy revealed only a few minor abnormalities. Surface invaginations of the lining mucosal cells were prominent and penetrated deeply into the cytoplasm of the cell (Fig. 3). There was slight separation of the lining surface cells especially at their bases, while a few lymphocytes, plasma cells and mononuclear phagocytes were seen between adjoining mucosal cells as well as in the *lamina propria.* Occasionally a few bacteria had adhered onto the lumenal surface of the mucosal cells. The specialized cells of the gastric glands did not exhibit any ultrastructural abnormality.

*Grade II:*—Scanning electron microscopy showed that the coarseness of the surface contours of the gastric mucosa was more prominent while the ostia of the gastric pits were much more dilated (Fig. 4) and often contained cell debris (Fig. 4). The lumenal surface of the lining cells varied in size and often the central zone of the lumenal surface was slightly protuberant. Microvilli were now being detected in this central area of the lumenal surface as well as in the more peripheral zones (Fig. 5).

The coarseness of the surface contours seen by scanning electron microscopy was reflected in samples subjected to transmission electron microscopy when again the irregular surface contours were evidence,

TABLE II

Age, Sex, Endoscopic Diagnosis and E.M. Grading of 20 Patients with Histologically Proven Chronic (Superficial) Gastritis

| Age (yrs.) | Sex (M/F) | Endoscopic diagnosis | Gastric biopsy | |
|---|---|---|---|---|
| | | | Histological diagnosis | E.M. Grading |
| 47 | F | CG | CG | II |
| 29 | M | AG | CG | II |
| 67 | M | CG | CG | II |
| 63 | M | CAG | CG | I |
| 26 | F | CG | CG | I |
| 69 | F | CAG | CG | II |
| 42 | F | CG | CG | II |
| 51 | M | CG | CG | II |
| 31 | M | AG | CG | I |
| 54 | F | CG | CG | II |
| 31 | M | CG | CG | II |
| 44 | M | CG | CG | I |
| 83 | F | CAG | CG | I |
| 58 | M | AG | CG | II |
| 56 | M | Normal | CG | I |
| 41 | M | Normal | CG | II |
| 70 | F | CG | CG | II |
| 82 | M | CAG | CG | II |
| 72 | F | CAG | CG | II |
| 40 | M | CG | CG | II |

AC = acute gastritis; CG = chronic gastritis; CAG = chronic atrophic gastritis.

being produced by unequal size of the lining mucosal cells (Fig. 6). The central part of the lumenal surface of these cells was somewhat protuberant while in the crevices between the surface mucus cells and in gastric pits bacteria were often found (Fig. 6). Many of these abutted directly onto the plasmalemma of the mucosal lining cell but were never seen within the cell. The basal portions of the mucosal lining cells were separated from each other due to an increase in the intercellular space which on many occasions also contained lymphocytes and less frequently granulocytes. Lymphocytes, plasma cells, granulocytes and mononuclear phagocytes were frequently found in the *lamina propria*. The specialized cells of the gastric glands were difficult to find and the majority of those found were of reduced dimensions possessing fewer cytoplasmic organelles than their normal counterparts.

TABLE III

MISCELLANEOUS GROUP

| Age (yrs.) | Sex (M/F) | Endoscopic diagnosis | Gastric biopsy | |
|---|---|---|---|---|
| | | | Histological diagnosis | E.M. grading |
| 22 | M | CG | HG | II |
| 40 | F | CG | FC | I |
| 69 | F | CAG | HFG | I |
| 79 | M | CG | HFC | I |
| 51 | F | AG | FG | I |
| 69 | M | CG | HFG | I |
| 29 | M | AG | HG | I |
| 36 | M | Normal | FG | I |
| 20 | F | Normal | Normal | I |

AG = acute gastritis; CG = chronic gastritis; CAG = chronic atrophic gastritis; HG = healed gastritis; FG = focal gastritis; HFG = healed focal gastritis.

*Grade III:*—Generally, the ultrastructural characteristics described under Grade II were also present in the samples placed in this group. There were, however, two additional features. Scanning electron microscopy indicated that all the lumenal surface of most mucosal surface lining cells possessed short microvilli (Fig. 7), while transmission electron microscopy revealed the appearance of electron dense mucosal lining cells. Some of these cells closely resembled those of the normal mucosal lining (Fig. 8) except for their electron density, their slightly reduced thickness and their lower content of mucus granules which were grouped into a cup shaped aggregate. In fact the fibrillar substructure of the secretion granules was identical (Fig. 8). Others possessed the ultrastructural characteristic of goblet cells with granules of a finely punctate substructure (Fig. 9). Still others displayed granules which characterized both these cell types (Fig. 10).

## RESULTS

The endoscopic, histological and ultrastructural assessments of the 33 patients studied are shown in Tables I, II and III. Comparison of the endoscopic diagnosis with the histological diagnosis of all 33 patients studied is shown in Table IV. Comparison of the histological diagnosis with the ultrastructural diagnosis is shown in Table V.

Ultrastructural changes as seen through the scanning and transmission electron microscope are shown in Figures 1-10. Histological changes are shown in Figures 11 and 12.

## COMMENT

The diagnosis of gastritis with the gastroscope has been reported by several authors with divergent results.[1, 7] In 1956 it was reported that histologically normal mucosa was found in 87% of cases with nor-

TABLE IV

COMPARISON OF ENDOSCOPIC DIAGNOSIS WITH HISTOLOGICAL FINDINGS

| Endoscopy | | Gastric biopsy (Histological diagnosis) | | | | |
|---|---|---|---|---|---|---|
| Diagnosis | No. | CAG | CG | AG | H/FG | Normal |
| CAG | 9 | 3 | 5 | 0 | 1 | 0 |
| CG | 14 | 0 | 10 | 0 | 4 | 0 |
| AG | 6 | 1 | 3 | 0 | 2 | 0 |
| Normal | 4 | 0 | 2 | 0 | 1 | 1 |
| Total | 33 | 4 | 20 | 0 | 8 | 1 |

AG = acute gastritis; CG = chronic gastritis; CAG = chronic atrophic gastritis; H/FG = healed or focal gastritis; N = normal.

mal mucosa on endoscopy with a semi-flexible instrument. The advent of the newer fiber-endoscope has not increased the diagnostic accuracy by any means since a recent report[9] showed that an endoscopically normal mucosa was histologically confirmed in only 68% of cases. The remaining cases showed various degrees of gastritis. The results of the present study confirm this finding since in four endoscopically normal mucosa only one was confirmed histologically, the remaining cases showing changes of gastritis. It would appear therefore that endoscopic diagnosis of normality in the gastric mucosa is unreliable. This would imply that in routine endoscopy it is not possible to say that the mucosa in the stomach is normal unless multiple biopsies of the gastric mucosa show a normal histology as well. This would further support the view that multiple biopsies should be obtained at routine endoscopies in spite of absence of specific abnormal findings.

Recent studies have indicated that it is difficult to diagnose gastritis endoscopically and one report has stated that gastritis can only be diagnosed with certainty on a histological basis.[13] In another recent report, the endoscopic diagnostic accuracy of gastritis was 68%.[9] Results of the present study show that the endoscopic diagnosis of chronic gastritis was confirmed in 10 out of 14 cases, the remaining four cases showing changes of either healed or focal gastritis. It is noteworthy that all 14 cases with an endoscopic diagnosis of chronic gastritis had changes of one sort or another on the histological examination. This indicates that although it is not possible to assess the chronicity of the gastritis, endoscopy can readily detect its presence. Of six cases in the present study diagnosed as acute gastritis on endoscopy, all showed changes of various degrees of gastritis but none had histological confirmation of acute gastritis. This would indicate that diagnosis of a specific type of gastritis like acute gastritis may be unreliable. Twenty cases in the present study were endoscopically diagnosed as either chronic gastritis or acute gastritis and the histology of these 20 cases all showed changes of gastritis of one type or another, indicating that the endoscopic diagnosis of gastritis without specifying the type would be more appropriate than dividing it into acute or chronic (see Table IV). It would appear therefore that endoscopically one should make a diagnosis only of gastritis without attempting to classify it in-

TABLE V

Comparison of Histological Diagnosis with E.M. Grading

| Gastric biopsy | | E.M. Grading | | |
|---|---|---|---|---|
| Diagnosis | No. | I | II | III |
| CAG | 4 | — | 1 | 3 |
| CG | 20 | 6 | 14 | — |
| H/FG | 8 | 7 | 1 | — |
| Normal | 1 | 1 | — | — |
| Total | 33 | 14 | 16 | 3 |

CG = chronic gastritis; CAG = chronic atrophic gastritis; H/FG = healed or focal gastritis.

to acute or chronic. With regard to chronic atrophic gastritis, however, of nine cases diagnosed on endoscopy, only three in the present study had histological confirmation. The remaining six cases had histological evidence of chronic healed or focal gastritis. The previously described criteria of atrophic gastritis, e.g. reduction in mucosal folding, would seem to be unreliable. It would therefore appear that endoscopic diagnosis of chronic atrophic gastritis is inaccurate and unreliable. Putting all these findings together it may be concluded that one should attempt only to diagnose the presence of gastritis in routine endoscopy, without attempting to classify the gastritis into various types endoscopically. Furthermore it appears that it is not possible to be certain about the normality of the gastric mucosa endoscopically without the availability of histological proof.

Scanning and transmission electron microscopy have been used in the assessment of gastric biopsies obtained with the fiber-endoscope.[10, 11] The results of these studies have given rise to a variety of ultrastructural changes, the significance of which remains to be fully clarified. Scanning electron microscopy provides a ready means of studying the damaged mucosa. Samples larger than can be examined by transmission electron microscopy, can be assessed. The contours of the mucosal surface, the size, shape and distribution of the gastric pits as well as the concentration and distribution of surface microvilli provide a quick means of grading the degree of damage. The only drawback to this procedure is the adequate removal of mucus from the surface of the mucosa. Mechanical removal of mucus as recommended by Fallah, et al,[11] proved the least damaging procedure.

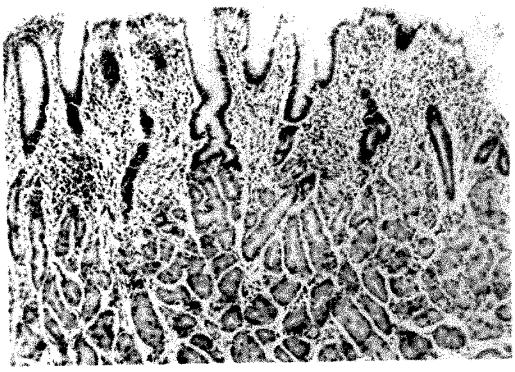

Fig. 11—Mild chronic gastritis (Hematoxylin and eosin, original magnification x100).

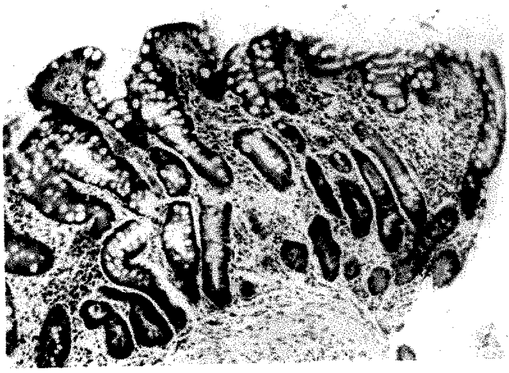

Fig. 12—Chronic atrophic gastritis with intestinal metaplasia (Hematoxylin and eosin, original magnification x100).

Generally our observations of gastric mucosa with evidence of severe chronic gastritis mirrored those of Fallah, et al. In addition, milder involvement could be detected by carefully assessing the size, shape and distribution of gastric pits; the general contours of the mucosa and the degree of concentration of the lumenal microvilli of the surface cells. The appearance of microvilli as distinct from the more bulbous surface projections in cases of chronic gastritis has already been noted.[11] The reason for their development is unclear but may be a means of mucus entrapment by the damaged cell.

The increase in surface microvilli is not as obvious in preparations viewed by transmission electron microscopy, especially in the less severely affected stomachs. Deep surface invaginations were, however, frequently found and in addition bacteria were commonly seen adhering to the surface of the lining cells but at no stage was phagocytosis observed. Deep indentations of the surface lining cells and the presence of intercellular edema near the basal portions of the lining mucus cells were other features of a damaged mucosa. The cause of the edema is not clear but may be related to a phlogistic response secondary to the etiological injury which may also partly explain the leucocytic infiltrate between the lining cells and in the *lamina propria.*

In the most severe instances the appearances of the electron dense lining cells was evident. These cells with their cup-shaped aggregates of mucus granules are part of the ultrastructural counterpart of the so called "intestinal metaplasia". The relationship to the goblet cells of the gastrointestinal tract, however, is complex. Apart from similarity in electron density some of these cells still resemble the normal mucosal lining cells. In fact, the ultrastructure of the mucus granule is similar to that of the normal mucosal lining cell and not that of the goblet cell seen elsewhere in the gastrointestinal tract. Others, on the other hand, resemble goblet cells, while a few have features of both. Possibly these graded structural stages relate to a similar functional and biochemical gradation.

The results of the present study show that there is good correlation between the severity of the histological changes and the degree of ultrastructural damage in chronic gastritis. There was, however, no evidence to show that electron microscopy could enhance the diagnostic accuracy or capability of light microscopy of the gastric biopsies obtained at routine endoscopy. It would appear that for routine endoscopy of patients with gastritis, electron microscopy would probably not be essential in the assessment of the biopsy material.

## ACKNOWLEDGMENTS

Preparation of gastric biopsies for electron microscopy was performed by S. H. Wee, R. Horne and P. Williams of the Electron Microscopy Unit, Royal Perth Hospital. Endoscopy was carried out in the Gastroenterology Unit of Royal Perth Hospital.

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# Gallstone-linked Tubular Stenosis of the Common Bile Duct

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The transpancreatic segment of the distal common bile duct can be extrinsically stenosed by a pure gallstone-linked pancreatic disorder. It has a specific roentgen configuration—long, tubular and smooth. In two instances it was associated with severe suppurative complications.

Precholedochotomy cholangiography is required to identify such long segment benign tubular stenosis of the distal common bile duct as an indication for management alternatives and as a guide to judicious common bile duct exploration.

Tubular stenosis of the distal common bile duct is encountered as a specific complication of gallstone disease. The diagnosis can only be made by cholangiography. The clinical course is not predictable. These three cases indicate the range of clinical presentation and a common method of management.

## CLINICAL DATA

*Case 1:*—A 72-year old man was hospitalized for abdominal pain, chills, fever, jaundice and a tender right upper quadrant mass. The serum bilirubin was 2.4 mg./%. An operation was performed for acute suppurative cholecystitis. Because of the dense obfuscating inflammatory reaction the procedure was cholecystolithotomy and cholecystostomy.

The postoperative course was uneventful. This cholecystocholangiogram (Fig. 1) was obtained on the tenth postoperative day. There is uniform stricture of the full length of the transpancreatic portion of the common duct. The supraduodenal duct is dilated and the saw toothing is a roentgen sign of cholangitis. Contrast material is voided into the duodenum. The pancreatic duct is not visualized. There are no pancreatic calcifications and no residual calculi. The cholecystostomy tube was left *in situ*. Five weeks later a cholecystectomy was performed. The choledochoduodenal passage pressure measured 35 cm. of saline on the Caroli manometer (normal 13 ± 7). There were no intraductal calculi and no acute cholangitis at this time. A side-to-side choledochoduodenostomy was performed. The postoperative course was benign and the patient was asymptomatic three years later.

*Case 2:*—This 72-year old male diabetic had a long history of biliary calculus disease. Surgical procedures had not been advised because of severe pulmonary insufficiency based on emphysema. He was admitted with shaking chills, fever to 40° C, jaundice and upper abdominal pain. Surgery performed within 24 hours revealed severe acute and chronic cholecystitis with suppurative cholangitis, multiple small common bile duct calculi and focal gangrenous areas in the supraduodenal common bile duct. The gallbladder was removed. The common duct was cleared of calculi. Because of the focal choledochal necrosis T-tube intubation was elected rather than

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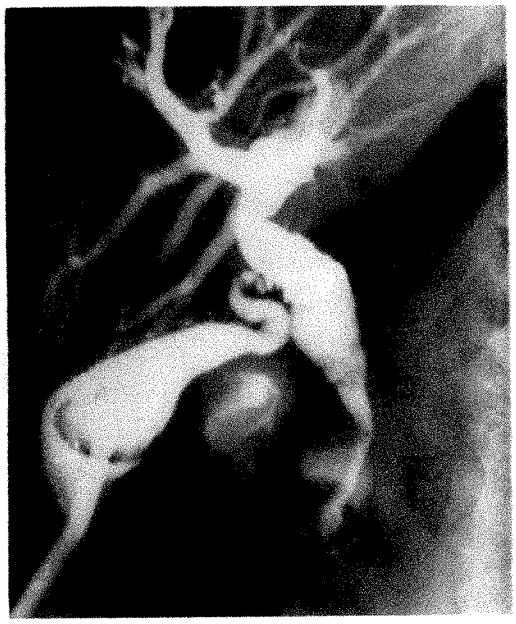

Fig. 1—This cholecystocholangiogram was performed through the cholecystostomy tube. The gallbladder is normal. The common duct contains calculi. There is persistent tubular stricture of the distal choledochus with proximal dilatation. Contrast material does enter the duodenum. There are no pancreatic calcifications.

primary choledochoduodenostomy. (Incidentally, this is the third instance of gangrenous emphysematous supraduodenal cholangitis that this institution has encountered.) An intraoperative cholangiogram (Fig. 2) shows no residual calculi and no areas of pancreatic calcification. There is a long tubular stricture of the transpancreatic portion of the common bile duct with marked dilatation of the supraduodenal choledochus. The pancreatic duct is visualized and its caput segment is dilated and contains the same type of calculi as were found in the common bile duct.

Postoperatively the common duct passage pressure was 38 cm. of saline. When the T-tube was clamped the patient became febrile and leaked bile. Six weeks later a choledochoduodenostomy was performed and the T-tube was removed. The patient died three months after discharge of cardiopulmonary disease. He had been without biliary symptoms.

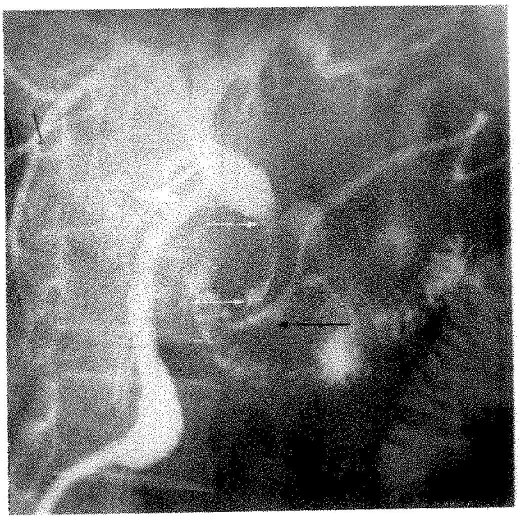

Fig. 2—This T-tube cholangiogram demonstrates a tubular stricture (white arrow) of the distal common bile duct with proximal dilatation. The black arrow indicates a slightly ectatic segment of the pancreatic duct. There are no pancreatic calcifications.

*Case 3:*—A 52-year old man had several episodes of biliary colic. Cholecystogram showed a functioning gallbladder with many small stones. The bilirubin was normal. At operation the diseased gallbladder was removed and a cystic duct cholangiogram performed (Fig. 3). There is marked long segment narrowing of the transpancreatic portion of the common bile duct. There were no duct stones and the saline passage pressure was 20 cm. of water. Because the duct aspirate, blood studies and manometric determinations were normal, no ductal decompression was undertaken. The patient has been asymptomatic for five and one half years. An intravenous cholangiogram done one year postoperatively revealed slight widening of the still stenotic distal common bile duct and a less disproportionate discrepancy with the proximal bile ducts.

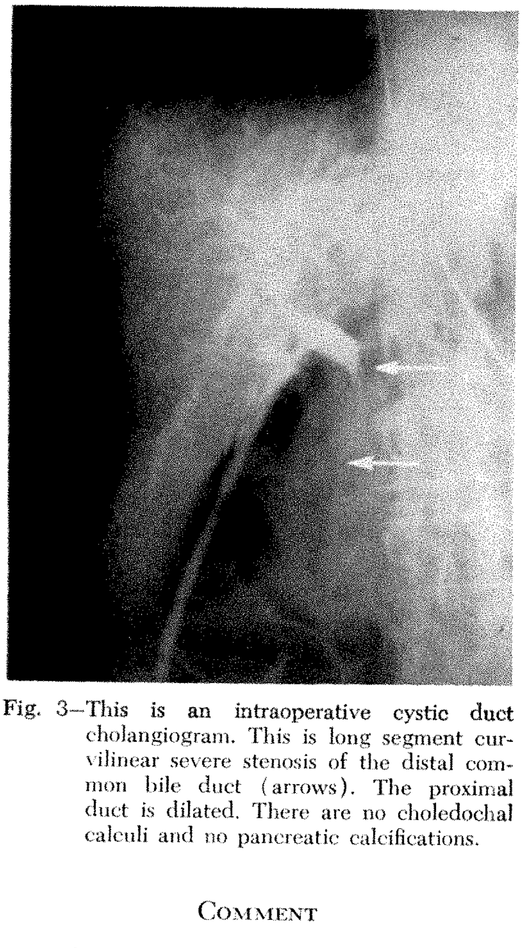

Fig. 3—This is an intraoperative cystic duct cholangiogram. This is long segment curvilinear severe stenosis of the distal common bile duct (arrows). The proximal duct is dilated. There are no choledochal calculi and no pancreatic calcifications.

## COMMENT

There are several features of this disorder that these three patients had in common: long-standing symptoms of gallstone disease, no alcohol abuse, similar cholangiographic pattern, no pancreatic calcification, elevated choledochoduodenal passage pressure and the absence of an antecedent anamnestic event that could be interpreted as acute pancreatitis. Two presented with suppurative complications and responded satisfactorily to incontinuity choledochoduodenostomy.

The diagnosis of tubular stenosis of the common bile duct can only be made by cholangiography. There is no way of reliably establishing the preoperative or intraoperative diagnosis by palpation or gross inspection alone.

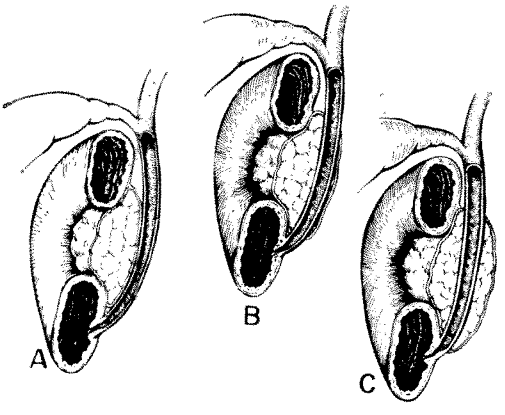

Fig. 4—(A) In this extrapancreatic position the lumen of the common duct is not affected. (B) In the intracapsular lay, the duct can be angulated but it is not compressed. (C) Where the duct passes through the pancreas the lumen can be compressed for part or all of its course. (From, Schein CJ, Stern WZ, Jacobson HG: *The Common Bile Duct Operative Cholangiography, Biliary Endoscopy, Choledocholithotomy*, Springfield, Charles C Thomas, 1966.

*Clinical features:*—The high male incidence has been commented upon by others. The pancreatic component is not suspected by past history, the plain film demonstration of pancreatic lithiasis or by unusual gross findings at operation. Two of the three patients were septic, the diabetic with advanced necrotizing cholangitis. In the third patient an equal degree of stenosis was not paralelled by an infectious complication. That patient was younger and the duration of his illness was brief. In terms of the total picture common duct stones were present in one, cholangitis in two but the anatomic changes were uniform.

*Cholangiographic features:*—The supraduodenal segment of the common duct is dilated. There is a long segment tubular stenosis involving the entire infraduodenal choledochus in the area where it courses through the pancreas. This stricture zone is smooth, of uniform caliber, and free of saw toothing (cholangitis) or calculi. It is assumed that this is the result of compression by the surrounding pancreas. These are the features of extrinsic compression. In each instance the obstruction was incomplete and contrast material traversed the stenotic area to enter the duodenum. By its length and symmetry, the roentgen pattern is clearly different from that encountered in cancer of the pancreas of cancer of the bile duct. This is likewise not the area nor the pattern of iatrogenic bile duct injury. Two of these strictures were dynamically significant in terms of manometry and as the cause of proximal dilatation. All were associated with proximal dilatation. The lesion is so specific that biopsy confirmation is not required.

The anatomic basis for this compression is that in about 70% of individuals the common bile duct passes through the pancreatic parenchyma. Hence any swelling or fibrosis in the head can compress the common bile duct. Where the duct courses extraparenchymally either intra- or extracapsular the duct will be displaced or angulated rather than compressed (Fig. 4).

*Management:*—The surgical goal is the removal of the present etiologic factor and the decompression of the hypertensive proximal duct. The former is accomplished by cholecystectomy and choledocholithotomy and the latter by side-to-side in continuity choledochoduodenostomy. This is best accomplished by creating a stoma that is at least 2.5 cm. in width. To this end the bile duct is opened vertically and anatomosed horizontally. A single layer anastomosis is adequate. Transductal splinting is not required.

Gallstone-linked long segment tubular stenosis of the distal duct is an uncommon disorder. It has been described in alcoholics by Warshaw, et al[1] and as a cause of obstructive jaundice without biliary disease by McCollum and Jordan.[2] In Larhen's review[3] of benign lesions affecting the postmortem cholangiogram compression of the common duct was encountered in four of 12 patients with pancreatic fibrosis. He comments that the sheath of a sword configuration is so characteristic that the diagnosis of pancreatic fibrosis can be made confidently.

The demonstration of a dilated common bile duct is an indication of an existing or past obstructive factor. Tubular stenosis of the distal duct is an uncommon disorder that can only be demonstrated cholangiographically. This documentation also avoids the potential perforation of unmonitored exploration of the stenosed segment and indicates that proximal decompression may be required for suppurative complications.

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# Hyperhaptoglobinemia and Carcinoma of the Gallbladder

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Cancer of the gallbladder is an uncommon malignancy which is seldom diagnosed early and often denotes a poor prognosis. Two reported cases describe the association of hyperhaptoglobinemia (> 700 mg./dl.) and advanced carcinoma of the gallbladder. When a patient presents with liver involvement from metastatic adenocarcinoma of suspected gastrointestinal origin and a markedly elevated serum haptoglobin (> 700 mg./dl.), it is suggested that a high index of suspicion be held for carcinoma of the gallbladder.

Cancer of the gallbladder is an uncommon malignancy which is seldom diagnosed early and often denotes a poor prognosis.[1] Recently, we have observed an association between a marked elevation of serum haptoglobin and carcinoma of the gallbladder in two patients. It is speculated that this association may help establish the diagnosis of advanced gallbladder carcinoma earlier, thus obviating the need for unnecessary exploratory surgery.

## Case Reports

*Case 1:*—A 69-year old white female presented to William Beaumont Army Medical Center with abdominal pain and mid epigastric fullness. Physical examination revealed right upper quadrant tenderness and a palpable liver 4 cm. below the sternum. Due to nonvisualization of the gallbladder with oral and intravenous cholecystograms, an exploratory laparotomy was performed with the presumptive diagnosis of acute cholecystitis. At surgery, however, a moderately well differentiated adenocarcinoma of the gallbladder was found with local extension to the liver. Because of this advanced disease, no debulking procedure was done. Two weeks postoperatively, the serum haptoglobin was 830 mg./dl. utilizing the standard technic of radial immunodiffusion (normal: 50-220 mg./dl.). Subsequent treatment consisted of radiation (3,000 rads) to the tumor site as well as weekly intravenous 5-fluorouracil (400 mg.). This therapy was to no avail and the patient died with diffuse metastatic disease 15 weeks following surgery. Shortly before death, the serum haptoglobin had fallen to 660 mg./dl.

*Case 2:*—A 51-year old white female presented to William Beaumont Army Medical Center with right upper quadrant pain, weight loss and jaundice. Physical examination revealed a nodular, firm palpable liver 12 cm. below the right costal margin. Liver biopsy from peritoneoscopy established a diagnosis of metastatic poorly differentiated adenocarcinoma of possible gastrointestinal origin. Gross thickening of the gallbladder wall as well as a suspicious mural defect were present on the oral cholecystogram. In view of our experience with

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

TABLE I

SERUM HAPTOGLOBIN VALUES IN VARIOUS MALIGNANCIES

| Primary tumor site or type | No. | Mean (mg./dl.) | Range (mg./dl.)* |
|---|---|---|---|
| Colon | 19 | 258 | 33-570 |
| Pancreas | 6 | 195 | 110-280 |
| Stomach | 4 | 206 | 84-270 |
| Liver | 3 | 154 | 20-360 |
| Gallbladder | 2 | 775 | 720-830 |
| Esophagus | 1 | 290 | 290 |
| Lung | 19 | 330 | 68-580 |
| Breast | 16 | 218 | 66-560 |
| Kidney | 3 | 719 | 440-1200 |
| Prostate | 2 | 226 | 92-360 |
| Testicle | 2 | 265 | 160-370 |
| Ovary | 1 | 275 | 275 |
| Lymphoma | 4 | 243 | 150-460 |
| Sarcoma | 2 | 235 | 150-320 |
| Malignant melanoma | 1 | 98 | 98 |

*Normal: 50-220 mg./dl.

Case 1, a haptoglobin was obtained and was 720 mg./dl. Treatment consisted, again of radiation (2,520 rads) to the primary site in addition to weekly intravenous 5-fluorouracil (600 mg.). Two months post-radiation, the haptoglobin had decreased to 516 mg./dl. Thirty-two weeks following the diagnosis, the patient died of progressive metastatic disease. At autopsy, the suspected clinical diagnosis of carcinoma of the gallbladder with liver involvement was confirmed. Homogenized tumor tissue had no detectable haptoglobin.

Additional serum haptoglobin values were obtained in 83 other patients with a variety of malignancies (Table I). Of note, only three patients had values over 700 mg./dl., the two with gallbladder carcinoma and one patient with renal cell carcinoma.

## COMMENT

Haptoglobin is an alpha-2 globulin which is synthesized in the liver. Elevated levels occur in a wide spectrum of disorders including infection, connective tissue diseases and malignancy.[2] The increased production in these states remains unexplained. Owens, et al,[2] reported increased mean serum haptoglobins (216 mg./dl. with a normal mean of 93 mg./dl.) in 54 patients with carcinoma although the primary tumor sites were not identified. In addition, mean haptoglobin values were not different in patients with and without metastases. Furthermore, the association of hyperhaptoglobinemia and renal cell carcinoma has been noted by several authors.[3-5]

This finding of hyperhaptoglobinemia in two patients with advanced gallbladder cancer is quite interesting. In view of Owens and co-worker's[2] observation that in 61 patients with biliary obstruction the mean serum haptoglobin was 190 mg./dl. with a range of 19-410 (normal: 10-220 mg./dl.), it seems unlikely that biliary obstruction secondary to tumor could account for the elevated haptoglobins in our cases. In addition, a mean haptoglobin level of 169 mg./dl. with a range of 51-350 mg./dl. was found in four patients with documented cholelithiasis studied at William Beaumont Army Medical Center. Tumor production of haptoglobin also seems implausible since we were unable to detect any haptoglobin in the homogenized tumor tissue in Case 2. The presence of liver metastases also probably does not account for these elevated levels since three patients with primary hepatocellular carcinoma had only a mean serum haptoglobin of 154 mg./dl. with a range of 20-360 mg./dl. Therefore, the most plausible mechanism seems to be increased liver production secondary to an ill-defined stimulus, perhaps close proximity, from the cancerous gallbladder.

Although no firm conclusions can be reached from only two cases, one observation is suggested. When a patient presents with liver involvement from metastatic adenocarcinoma of suspected gastrointestinal origin and a markedly elevated serum haptoglobin (> 700 mg./dl.), a high index of suspicion must be held for carcinoma of the gallbladder.

## ADDENDUM

Since the submission of this manuscript, we have encountered a third case of hyperhaptoglobinemia with advanced carcinoma of the gallbladder.

*Case 3:*—A 66-year old white female presented with right upper quadrant pain and jaundice. At surgery a well-differentiated adenocarcinoma of the gallbladder with extensive involvement of the common bile duct was found. Metastasis to the liver was not present. Two weeks postoperatively the serum haptoglobin was 720 mg./dl. Presently, the patient is being treated with radiation and chemotherapy (5-fluorouracil). This case further substantiates the point, noted in the text, that the presence of liver metastases probably does not account for the finding of hyperhaptoglobinemia associated with advanced carcinoma of the gallbladder.

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***Clinical Vignette***

# Meat Bolus Impaction of the Lower Esophagus Associated with a Paraesophageal Hernia

## SUCCESSFUL NONINVASIVE TREATMENT WITH INTRAVENOUS GLUCAGON

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Ferrucci and Long recently reported the relief of esophageal food impaction with the use of intravenous glucagon in three patients.[1] Our first experience in using this new procedure was very successful and gratifying.

The essence and purpose of this brief communication is to record and further substantiate the efficacy of a new treatment modality.

### CASE REPORT

A 52-year old nurse presented with complaints of repeated bouts of regurgitation and retching for 12 hours following a steak dinner. The patient was calm, yet very assertive about the nature of her problem, "A piece of steak is stuck in my esophagus". Vital signs were stable; the patient had a past history of hiatus hernia diagnosed in 1976.

Barium swallow disclosed characteristic signs of esophageal obstruction secondary to food impaction in the lower third of the esophagus (Figs. 1 and 2). The barium swallow was repeated under fluoroscopy in the upright position. Exactly six minutes after the intravenous administration of 1 mg. of glucagon (Fig. 2), rapid filming under fluoroscopy was performed and revealed the rapid passage of the meat bolus from the lower esophagus into the stomach. Descent of the column of barium above the meat bolus was accompanied by active esophageal motility in the presence of visible relaxation at the level of the esophagogastric junction.

A large barium filled paraesophageal hernia is described on films taken after relief of the obstructing meat bolus impaction (Fig. 2).

Following this procedure the patient was asymptomatic and she was discharged on a liquid diet to return for elective esophagoscopy and treatment planning.

### COMMENT

Commonly described lesions associated with obstructive food impaction of the

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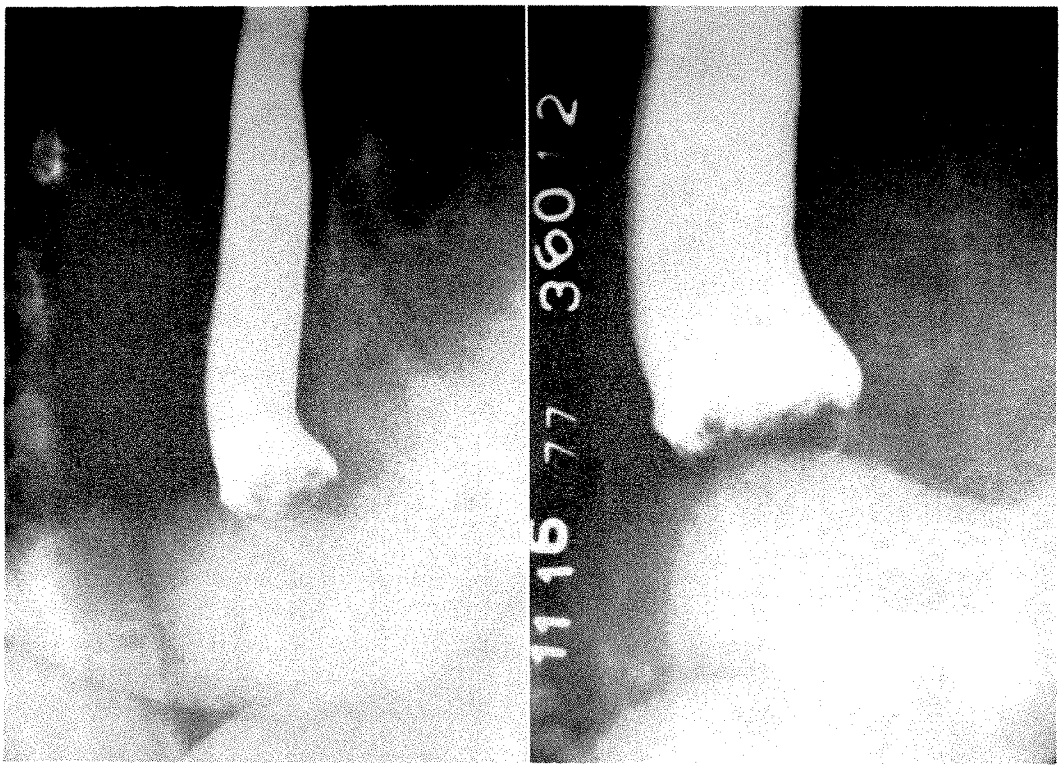

Figs. 1 and 2—Obstructing meat bolus in the lower esophagus with moderate esophageal distention above the radiolucent filling defect within the esophagus. Some inspissation of contrast material is seen about the obstructing intraluminal bolus.

esophagus include: 1. A tight mucosal ring; 2. carcinoma of the esophagus; 3. esophageal stricture; 4. esophageal spasm, achalasia and other motility disorders of the esophagus of various etiology including esophagitis and very commonly so called presbyesophagus of the elderly; 5. edentulous patients, frequently elderly, who ingest large, solid-particulate matter without adequate mastication.

The present case describes complete obstruction of the lower esophagus secondary to meat bolus impaction above a relatively rare type of hiatus hernia[2]—paraesophageal hernia. The activity and usefulness of glucagon intravenously and intramuscularly in gastrointestinal studies such as hypotonic duodenography and barium studies of the colon are well known.[3] The mechanism of action in the esophagus appears to be somewhat specific for the esophagogastric junction, effectively providing relaxation at this point and yet allowing esophageal peristalsis and motility to continue unaltered. The combination of relaxation at the esophagogastric junction, the hydrostatic pressure from the column of ingested barium in the upright position and active esophageal peristalsis, permit passage of the obstructing meat bolus.

The radiographs in this report illustrate a technic of pharmaco- and interventional radiology which precludes emergency esophagoscopy in obstructive esophagopathy. The attendant hazards of emergency esophagoscopy are avoided[4] and the patient, relieved of acute symptoms, may be further studied radiographically and endoscopically on an elective basis.

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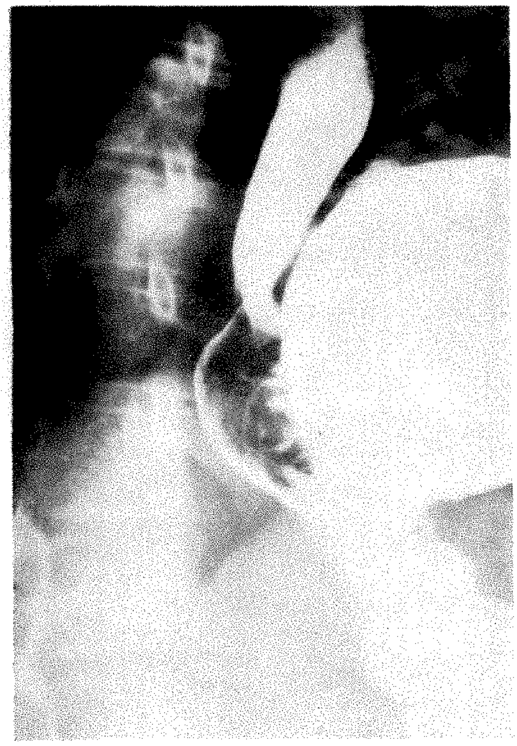

Fig. 3—Esophagram demonstrating free flow of contrast into the fundus of the stomach immediately after the passage of an obstructing bolus of meat, six minutes following the intravenous administration of 1 mg. of glucagon. Barium opacified a paraesophageal hernia.

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***Clinical Vignette***

# Stricture of the Esophagogastric Junction with Adjacent Extraluminal Cavity Following Radiation

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We report a radiation stricture of the esophagogastric junction with an adjacent extraluminal cavity formed secondary to radiation in a patient receiving 4,500 rads for a histiocytic lymphoma of the stomach. We suggest that the presence of a radiosensitive lymphoma may have undermined the normal reparative response to radiation of the esophagogastric junction and predisposed it to stricture and cavity formation at this dose of radiation.

Lymphomatous involvement of the esophagus is an unusual but now recognized presentation of gastrointestinal lymphoma.[1] As involvement of contiguous areas of stomach is the usual finding, radiation has been recommended as the therapeutic modality of choice because of its efficacy in the treatment of gastric lymphoma.[1,2] To date, no complications have been described. We report a case of lymphoma of the distal esophagus and contiguous stomach where the use of a total dose of 4,500 rads was associated with a radiation stricture of the esophagogastric junction and an adjacent extraluminal cavity whose wall and content suggested radiation necrosis.

## CASE REPORT

E. F., a 69-year old white woman was referred from another hospital for evaluation. She was well until February, 1976 when she noted the onset of progressive dysphagia to solids and liquids over the next six weeks, accompanied by weight loss. An upper gastrointestinal series performed two months later was reported as showing a malignant lesion of the lower esophagus. She was admitted to another hospital where endoscopy suggested a malignant lesion of the esophagogastric junction with extension into the stomach. A liver biopsy, however, showed only atypical cells. She subsequently underwent exploratory laparotomy at which time histiocytic lymphoma involving the distal esophagus, cardia and fundus was found. As this was felt to be unresectable, a a feeding gastrostomy was performed.

Beginning approximately two weeks after surgery, a course of radiation was begun during which time 4,500 rads was administered to the epigastrium and left upper quadrant over a six-week period. During this time, however, the patient complained frequently of emesis from the gastrostomy tube. An upper gastrointestinal series, per-

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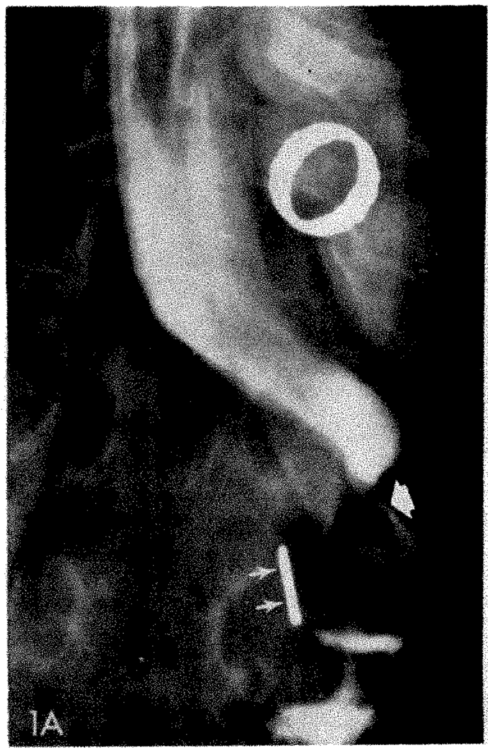

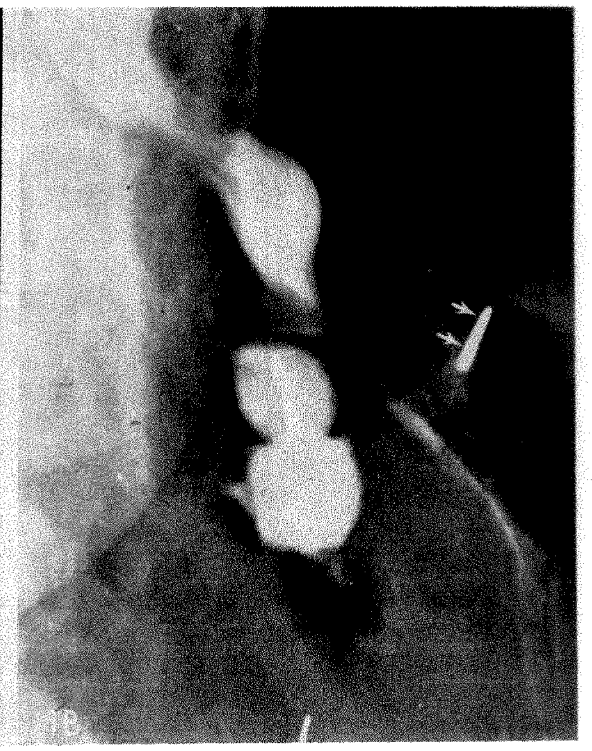

Fig. 1a—A Gastrografin esophagogram performed following the onset of pain and fever immediately after rigid esophagoscopy. The AP view shown here demonstrates a stricture (large arrows) as well as filling of an extraluminal cavity in the area marked by the clip (small arrows), previously occupied by histiocytic lymphoma.

Fig. 1b—An oblique view shows more complete filling of this extraluminal cavity along with displacement of the fundus (small arrows).

formed following the completion of radiation, showed a benign appearing stricture of the distal esophagus in the area where previously the lymphoma had been demonstrated. Over the next month she continued to lose weight and was referred for evaluation.

On admission, the patient appeared to be mildly cachectic. Laboratory data on admission was unrevealing as were other studies performed during her admission including an I.V.P., liver spleen scan, bone scan, bone marrow aspiration and core biopsies.

Fiberoptic endoscopy performed two days after admission revealed a tight esophageal stricture at 40 cm. from the incisors which could not be passed. The esophageal mucosa just proximal to the stricture was somewhat granular and telangiectatic appearing submucosal vessels were noted. The biopsies taken above the stricture showed only esophageal dysplasia felt to be secondary to irradiation.

As the clinical diagnosis at this time favored radiation stricture of the esophagus over recurrent tumor, esophageal dilatation was attempted; however, even a Puestow wire failed to achieve passage across the gastroesophageal junction. Rigid esophagoscopy was also tried which failed to pass the stricture. Immediately following rigid esophagoscopy, however, the patient began to complain of pain and fever. A Gastro-

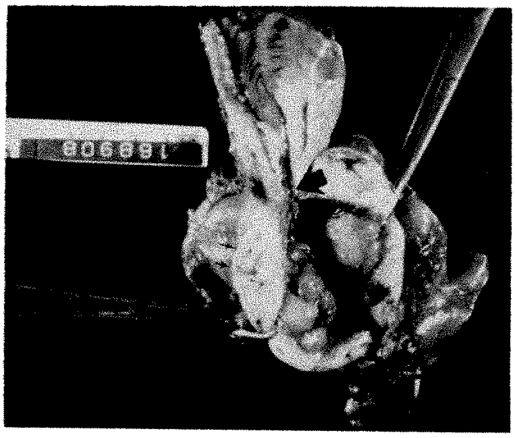

Fig. 2—The resected surgical specimen shows a stricture of the esophagogastric junction (large arrow) along with the wall of an extraluminal cavity, unroofed at the time of surgery containing 100 cc. of organizing necrotic material (small arrows).

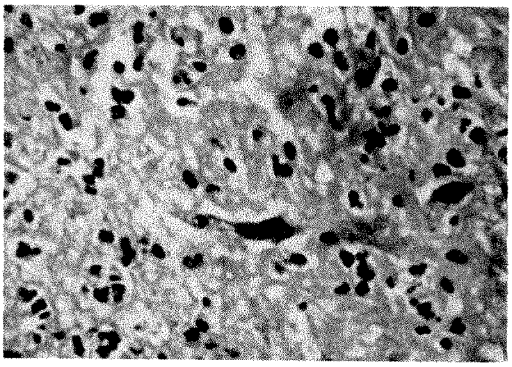

Fig. 3—Histologic examination of the cavity shows radiation fibroblasts in an acutely inflamed necrotic coagulum suggesting radiation necrosis (hematoxylin and eosin, original magnification x160).

grafin swallow performed on the following day demonstrated a stricture of the esophagogastric junction (Figs. 1a and 1b). Adjacent to the stricture was an extraluminal collection of contrast material in the area, marked by surgical clips, where previously the histiocytic lymphoma had been. This was thought to represent an acute perforation at the esophagogastric junction. She was explored six days later and an esophagogastrectomy was performed. Approximately 10 cm. of distal esophagus and some stomach was resected which demonstrated a stricture of the esophagogastric junction. In addition, a 1.4 × 2 × 1.3 cm. extraluminal cavity adjacent to the stricture was found (Fig. 2) which contained approximately 100 cc. of organizing, necrotic material. It was not cultured but it did not appear grossly purulent. There was no evidence of residual lymphoma. Histologic examination of the esophagogastric junction showed fibroblasts, subendothelial vacuolization in the large arteries and radiation fibroblasts consistent with a radiation stricture. The cavity showed radiation fibroblasts in an acutely inflamed necrotic coagulum (Fig. 3) suggesting radiation necrosis rather than an acute perforation.

Her postoperative course was unremarkable and the patient was discharged three weeks later. Subsequently, there has been no evidence of recurrent lymphoma.

## COMMENT

Two related complications occurred in this patient receiving radiation for esophagogastric lymphoma. These were a radiation stricture of the esophagogastric junction and the formation of an adjacent extraluminal cavtiy. Both of these complications appeared to be the result of radiation injury.

Radiation strictures of the esophagus have been well documented in the setting of high dose radiation, exceeding 6,000 rads,[3] administered in the treatment of oat-cell carcinoma of the lung[4] and carcinoma of the esophagus.[5] Radiation doses of less than 6,000 rads are not usually associated with stricture formation though, recently, doses of between 3,000 and 5,000 rads have been reported to produce esophageal strictures when radiation has been followed by chemotherapy utilizing Adriamycin, an agent capable of acting in a radiomimetic fashion.[6-8]

Short of combination chemotherapy with Adriamycin, doses of radiation of less than 6,000 rads only rarely produce radiation injury of the esophagus[3] and only dyspepsia and antral scarring when administered to the stomach.[9, 10] The dose of 4,500 rads received by our patient alone does not account for the finding of a radiation stricture of the esophagogastric junction. A clue to the susceptibility of this area to radiation injury, we feel, lies in the second complication, the finding at surgery of an extraluminal cavity adjacent to the radiation stricture. As the location of the cavity corresponded to that of the histiocytic lymphoma and its wall and content histologically showed radiation necrosis, we believe it most likely represents the space occupied by the histiocytic lymphoma before being entirely destroyed by radiation. The proximity of the cavity to the stricture and the involvement of the esophagogastric junction by lymphoma demonstrated by x-ray and at the initial surgery suggests that the presence of the lymphoma made this region unusually sensitive to radiation, possibly by interfering with the reparative response of the normal tissue to the dose of radiation administered.

As gastric perforation in the setting of gastric lymphoma occurs spontaneously,[11, 12] as well as following radiation,[13, 14] the origin of the extraluminal cavity, in our case, is not entirely clear though at no time prior to rigid esophagoscopy did the patient's course suggest perforation. As the content and wall of the cavity did not suggest it to be the result of acute perforation, we believe that the cavity had been formed prior to rigid esophagoscopy during the course of radiotherapy for the lymphoma. Rigid esophagoscopy could have undermined a tenuous separation between the stricture and the pre-existing extraluminal cavity allowing for the passage of Gastrografin into the cavity afterward. In addition, the force of the rigid esophagoscope against the wall of the cavity may have led to either bacterial contamination of the cavity or bacteremia from prior contamination. In either case, the picture simulating acute perforation which followed rigid esophagoscopy would have been produced.

The combination of a radiation induced stricture of the esophagogastric junction and a contiguous extraluminal cavity formed secondary to radiation necrosis has not, to our knowledge, been reported in the treatment of lymphoma of this area. We suggest that it be considered as a possible complication in the management of esophagogastric lymphoma if radiation is to be the principal therapeutic modality.

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***Clinical Vignette***

# Lymphosarcoma of the Duodenum Associated with Carcinoma of the Lung*

## FIVE-YEAR SURVIVAL

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The case presented describes a patient with lymphosarcoma of the duodenum associated with carcinoma of the lung. This emphasizes the basic problems which lymphosarcoma of the duodenum presents. They are vague symptoms until late in the course of the disease, the absence of early physical findings, the difficulty in interpretation of radiological studies and the frequent association with other primary malignancies elsewhere.

Carcinoma of the small bowel is more common in the duodenum, while sarcoma is more common in the distal small bowel.[1-4] Of the sarcomas, leiomyosarcomas and lymphosarcomas are the predominant lesions, the latter being more common.[5-10]

Lymphosarcoma of the duodenum is a rare occurrence. The Mayo Clinic[7] in a 25-year review reported 370 patients with small bowel malignant tumors, 61 in the duodenum with one lymphosarcoma. At Peter Bent Brigham[11] of 115 cases of small bowel malignancy, 19 were located in the duodenum with no case of lymphosarcoma. Bruno and Fein[12] described one case of lymphosarcoma in 13 malignant tumors of the duodenum (excluding ampullary lesions). Cortese and Cornell[13] reviewed 35 patients with primary duodenal malignancy at New York Hospital. There was not a single case of lymphosarcoma. Serrano and McPeak[8] found one lymphosarcoma in 21 malignancies of the duodenum.

Individual case reports of lymphosarcoma of the duodenum are sparse in the literature. In 1935 Prey, et al[14] presented one case and collected 61 authentic cases since 1877. Present[15] in 1939 added two of his own cases and cited three additional cases in the literature. His cases were proven by biopsy, the lesions not having been resected. In 1969 Madhavan and Balasubrahmanyan[16] reported one case which was diagnosed at autopsy. More recently, Aschner and Bercu[17] presented three instances of lymphosarcoma of the third part

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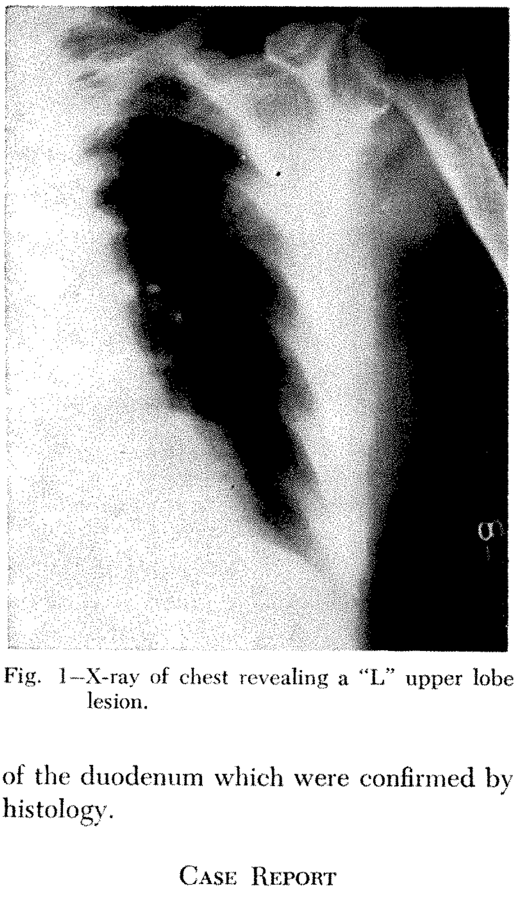

Fig. 1—X-ray of chest revealing a "L" upper lobe lesion.

of the duodenum which were confirmed by histology.

## Case Report

The patient is a 68-year old white female admitted to Beth Israel Medical Center on 31 July 1972, with a history of hematemesis and melena. Her illness commenced in April, 1972 when she had her first episode of hematemesis while on vacation in California. There was no history of abdominal pain, nausea or vomiting but she had been experiencing post prandial bloating for a few months. She was hospitalized in California where a routine chest x-ray revealed a left upper lobe lesion (Fig. 1) and upper gastrointestinal x-rays were interpreted as showing a duodenal ulcer. She was treated medically with blood replacement and on a bland diet she showed no further evidence of gross bleeding.

She returned to New York and was admitted to another hospital in June, 1972 for study of the left upper lobe lesion of the lung. She subsequently underwent a left thoracotomy and a left upper lobe lobectomy. The pathological diagnosis was "alveolar cell carcinoma of the lung" (Fig. 2). Postoperatively she recuperated well from her surgical procedure but her general medical condition was poor. She constantly experienced belching, bloating and anorexia and was anemic. Gastrointestinal x-rays were performed prior to the pulmonary surgery and were interpreted as showing a duodenal diverticulum. She was discharged on an antacid regime.

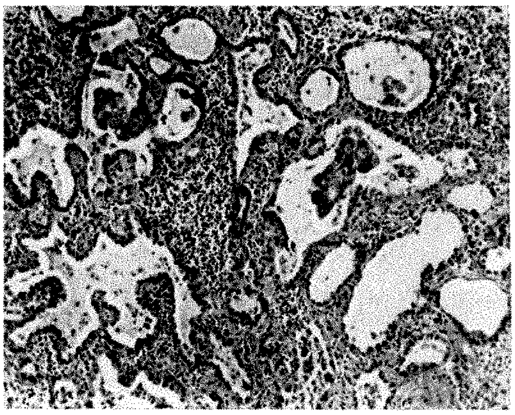

Fig. 2—This light micrograph of the lung tumor displays the epithelial character of this neoplasm. A tendency to form glands is evident, as are mucus secretion and alignment of the neoplastic cells along the preexisting alveolar structures. There is a moderately heavy inflammatory infiltrate in the background (Hematoxylin and eosin, original magnification x71).

After her discharge from the second hospital, her digestive symptoms persisted, she had another episode of hematemesis and sought further advice. Gastrointestinal x-rays performed in July, 1972 by one of us (L. A. W.) revealed a filling defect of the descending portion of the duodenum (Fig. 3). The contours of this portion were irregular and showed filling defects. The duodenal bulb was normal. The impression was of an infiltrating tumor of the second

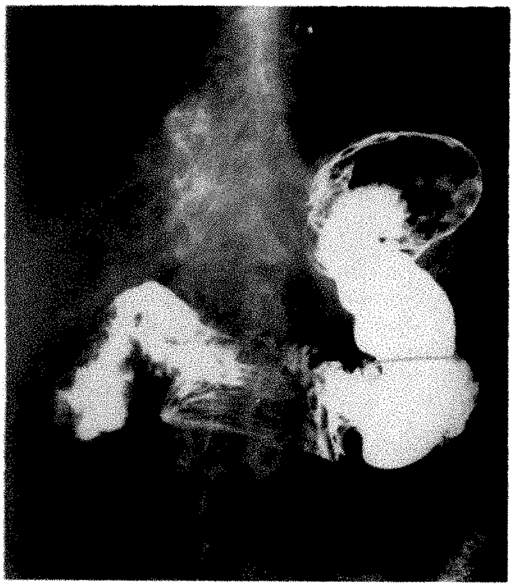

Fig. 3—Gastrointestinal x-rays revealing a filling defect of the descending portion of the duodenum.

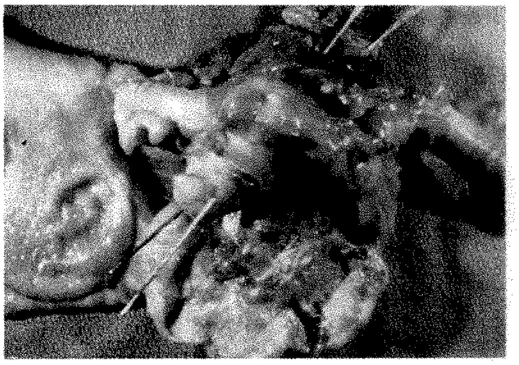

Fig. 4—The photograph displays the gross appearance of the lymphoma of the duodenum as viewed from its luminal aspect. The tumor is large, centrally ulcerated and has raised, rolled margins that protrude into the lumen. The probes are placed in the common bile duct and the main pancreatic duct and it can be seen that the tumor envelops both. The duodenum proximal to the tumor (left) is moderately dilated as compared to the bowel distal to the tumor (right).

portion of the duodenum. Gastroduodenoscopy was performed on an ambulatory basis at Beth Israel Medical Center. This revealed a fungating ulcerating lesion of the second portion of the duodenum. A biopsy taken at this time was interpreted as "poorly differentiated adenocarcinoma". She was then admitted to Beth Israel Medical Center on 31 July 1972.

Physical examination on admission revealed a well developed, well nourished white female in no acute distress. Her blood pressure was 100/60; pulse, 88; regular sinus rhythm; temperature, 37° C; respiration, 16/min. Examination of the head, neck, heart and lungs were not remarkable. The abdomen was soft, nondistended and nontender with the liver edge palpable two fingerbreadths below the right costal margin. No other masses or organs were palpable and there was no costovertebral tenderness. Rectal examination was not remarkable. Stool guaiac was positive.

Laboratory studies included a CBC; Hgb., 8.3 gm.%; Hct., 35.7; WBC, 8,700 with a normal differential. Urine analysis was normal; bile, negative. Chemistries were: glucose, 108 mg.; BUN, 32 mg., total protein, 5.2 gm.; albumin, 2.3 gm.; total bilirubin, 2.5 mg. Alkaline phosphatase, 365 units; LDH, 250; SGOT, 450 and SGPT, 128. Stools were persistently guaiac positive.

The patient was transfused with four units of blood. Serial enzymes showed persistent elevation of the alkaline phosphatase to levels of 200-350 and a mildly elevated SGOT to 300. The bilirubin remained elevated to 3.5 mg. She continued to bleed slowly, requiring several transfusions to maintain a Hgb. over 10 gm.%. By 21 August 1972, the alkaline phosphatase had risen to 700 units and the SGOT was elevated to 500 units. Physical examination at this time revealed the liver to be unchanged in size but there was now a fullness in the right upper quadrant, approximately 4 × 6 cm. in size, not tender or pulsatile.

On 30 August 1972 she underwent an exploratory laparotomy which revealed a

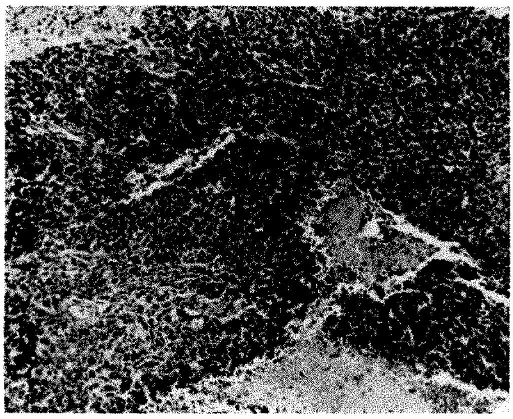

Fig. 5—The light micrograph reveals the monomorphic pattern of the tumor cells with foci of necrosis evident in the lower portion of the field (Hematoxylin and eosin, original magnification x88).

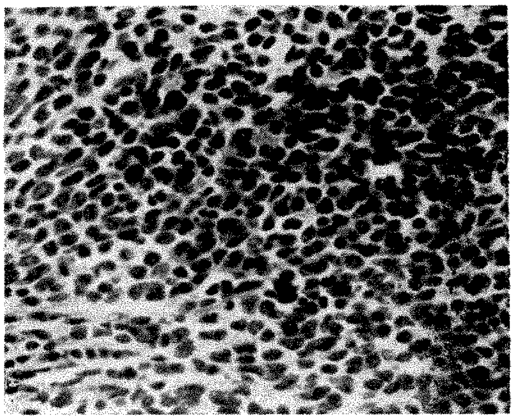

Fig. 6—This light micrograph exhibits the essentially monomorphic character of the cells comprising the duodenal lymphoma. The cytoplasm is uniformly scanty but the nuclei range in size and density. Some resemble nuclei of mature lymphocytes, while others look like the nuclei of moderately differentiated lymphoid cells with less compact chromatin and perceptible nucleoli. There are scattered mitoses among the tumor cells in this field (Hematoxylin and eosin, original magnification x178).

tumor mass of the second portion of the duodenum. The mass was firmly adherent to the head of the pancreas but freely moveable and not fixed to surrounding structures. The biliary tree and gallbladder were not distended. There was no evidence of any distant spread. The distal portion of the stomach, the duodenum and proximal jejunum together with the head of the pancreas were removed *en bloc* (Fig. 4). An end-to-end pancreaticojejunostomy and an end-to-side choledochojejunostomy and gastrojejunostomy were carried out to reconstitute the gastrointestinal tract. Because of the narrowed common duct, the biliary anastomosis was drained with a T-tube.

Postoperatively the patient's course was uncomplicated. A T-tube cholangiogram on the 14th postoperative day revealed free flow of the dye into the jejunum. The T-tube was removed, and the patient was discharged on the 16th postoperative day.

The pathologic report revealed a huge, yellowish, ulcerating tumor mass measuring 10.5 × 7.5 cm. and covered almost the entire circumference of the duodenal wall. The ampulla of Vater was identified in the center of the ulcerated tumor and was probe patent. It was surrounded by a firm, yellowish, elevated tumor mass. The mucosa of the duodenum showed a normal rugal pattern. The pancreatic duct measured 0.52 cm. in diameter and was patent. Microscopic diagnosis was "primary lymphosarcoma of the duodenum" (Figs. 5 and 6). The biopsy taken during endoscopy was then reviewed and was found to conform with this diagnosis.

Following discharge, the patient received a course of radiotherapy (1,400 rads). She is alive and well five years postsurgery.

## COMMENT

Next to adenocarcinoma, lymphosarcoma is the most common neoplasm of the small intestine and the duodenum is the least common site of occurrence of the tumor.[2, 4, 11, 12] Rare case reports of duodenal lymphosarcoma are published in the literature.[14-16] The diagnosis is often delayed, since early in the stage of the disease symptoms are insidious and nonspecific. Physical findings are frequently absent and radiological studies are often inaccurate unless carefully performed and interpreted. Deformities of the duodenum are often thought to be secondary to peptic ulceration or diverticulum. The presence of mucosal thickening, irregular polypoid filling defects that may narrow the lumen and rigidity of the duodenal wall should lead to a suspicion of duodenal lesions other than ulcer. Aschner and Bercu[17] describe the presence of a large triangular crater which they interpret as a pathognomonic sign of lymphosarcoma. Until the fiberoptic gastroduodenoscope was developed, radiological studies were the primary procedures employed to diagnose neoplastic lesions of the duodenum. With the ever widening use of the endoscope, however, a new dimension has been added to the investigation.[18] In the hands of the experienced endoscopist, it is a safe and reliable method of distinguishing between benign and malignant lesions. Laufer, et al[19] compared radiologic and gastroscopic diagnoses and in 175 patients examined by standard gastrointestinal x-rays, there were 39 radiologic errors (22%).

There appears to be a significant incidence of other primary malignancies in patients with small bowel neoplasm. Reyes and Talley[20] reported an incidence of a second primary outside the small intestine in 17.7% compared to 0.33% noted in the average population. Ostermiller, et al[4] found an incidence of a second neoplasm in 12 of 61 cases and Strauch[21] in six of 47, the associated lesions being located in the prostate, colon, breast, liver or uterus. As noted, our patient had a primary neoplasm of the lung.

As in all patients with neoplasm of the small intestine, the operation for lymphosarcoma entails generous resection of bowel and mesentery to include adjacent lymph glands. For lesions of the duodenum, adequate management requires a radical pancreaticoduodenectomy. It is our feeling that postoperative radiation is indicated, especially if glands are involved or the lesion extends to the line of resection. Weaver and Batksakis[22] question the value of radiotherapy where lymph glands are negative and the tumor has been removed.

The prognosis of small bowel lymphoma is poor. In Kahn's [23] series of 20 cases, only one is well six years after therapy. Nagvi, et al[24] reported a five-year survival of 38% in operative cases including nonresectable cases while Nicoloff, et al[3] reported a five-year survival of 22%. The prognosis of duodenal lymphosarcoma patients is worse. Almost all cases reported were not resectable at surgery or diagnosed at autopsy. The patient presented is now five years postsurgery and radiotherapy and is doing well.

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***Clinical Vignette***

# Intramural Hematoma of the Gastric Cardia

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A case of intramural hematoma of the gastric cardia occurring in a young woman with *S.L.E.* and on warfarin is presented and discussed. This unusual case illustrates the importance of careful evaluation of radiological mass lesions of the cardia.

## INTRODUCTION

Intramural hematoma affecting the gastrointestinal tract is well documented. The first description, in 1838, was of an intramural hematoma of the duodenum in a patient who had suffered abdominal trauma.[1] Since that time, several hundred reports have appeared in the world literature.[2, 3]

The first case of intramural hematoma of the stomach was reported in 1965;[4] six other cases have since been reported.[5-8] None of these hematomas occurred in patients who were on anticoagulants.

This paper describes a young woman with known systemic *lupus erythematosus* who developed an intramural gastric hematoma while taking warfarin.

## CASE REPORT

J. F., a 24-year old single female, was admitted through the emergency room of the Vancouver General Hospital with a three-day history of constant, "tearing", epigastric pain, unrelieved by food or antiacids. She complained of chills, and vomited thick white material containing flecks of blood four hours before admission.

Past history included three episodes of deep venous thrombosis in the course of one year, the most recent occurring one month before the present admission. On that occasion she was found to have a positive antinuclear factor, *L.E.* cells, and a high titer of DNA antibody in her blood. Since then she had been taking warfarin 2.5 mg. daily, irregularly.

Examination revealed that her temperature was 37.7° C. orally, pulse rate was 68/min. and there was diffuse epigastric tenderness without guarding or rebound tenderness. No mass was palpable and otherwise physical examination was negative.

Urinalysis showed +4 protein with 11-20 red blood cells. Blood count showed 2.7 x $10^3$/cu. mm.; white blood cells, with a differential of 42% neutrophils, 20% staff cells, 36% lymphocytes, 2% monocytes. Hemoglobin was 12.1 gm.% and the platelet count was 180,000/cu. mm. The

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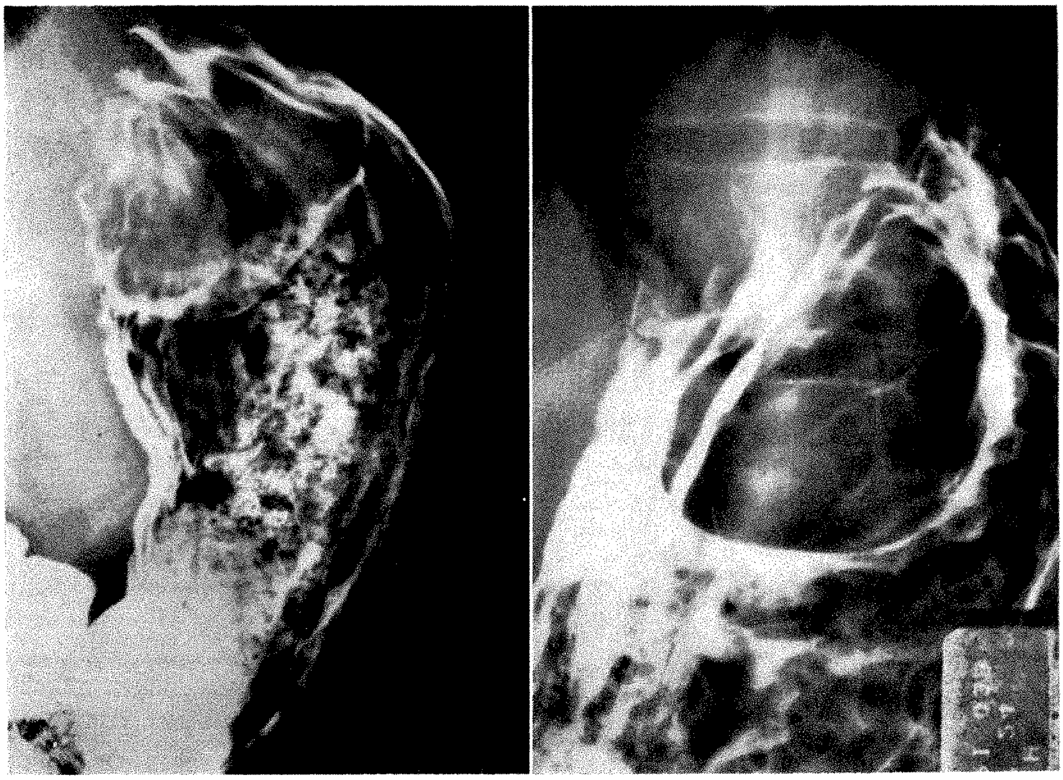


Figs. 1a and 1b—Upper gastrointestinal series showing large cardia mass with normal mucosal pattern.

ESR was 108 mm./hr.; prothrombin time, 18.5 seconds (control of 12 seconds), and activated PTT was 57 seconds (normal 30-45 seconds). Numerous *L.E.* cells were found. The electrolytes, BUN, creatinine, ECG and chest x-ray were normal.

An upper gastrointestinal series showed a 7 cm. diameter extramucosal intramural lesion of the cardia of the stomach (Fig. 1). No esophageal reflux or hiatus hernia could be demonstrated.

Gastroscopy was performed, which showed an approximately 8 cm. diameter, well circumscribed, plum-colored lesion arising from the greater curvature aspect of the cardia (Fig. 2). No mucosal ulceration was seen. The esophagus, the remainder of the stomach and the duodenum appeared normal. Biopsies taken of the lesion showed nonspecific acute and chronic inflammation. The possibility that this lesion was a hematoma was considered and it was decided to stop the warfarin and observe her. Over the following week her symptoms subsided, and a repeat upper gastrointestinal series was performed. This showed a completely normal gastric cardia and fundus (Fig. 3). Repeat gastroscopy showed a boggy, edematous-appearing cardia which tended to bleed easily but no mass was seen.

During her stay in hospital, a classical anticoagulant associated with *S.L.E.* was found.

## COMMENT

Tumors arising in the region of the gastric cardia present a most interesting

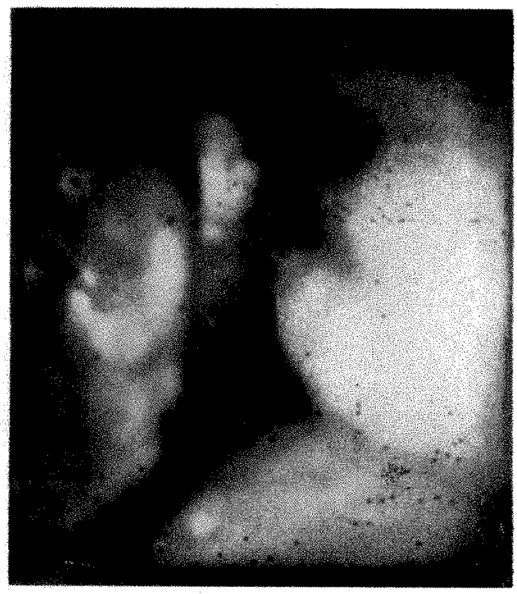


Fig. 2—Endoscopic appearance of cardia mass which occupies most of the left half of the field. Normal esophagogastric junction is seen at the right.

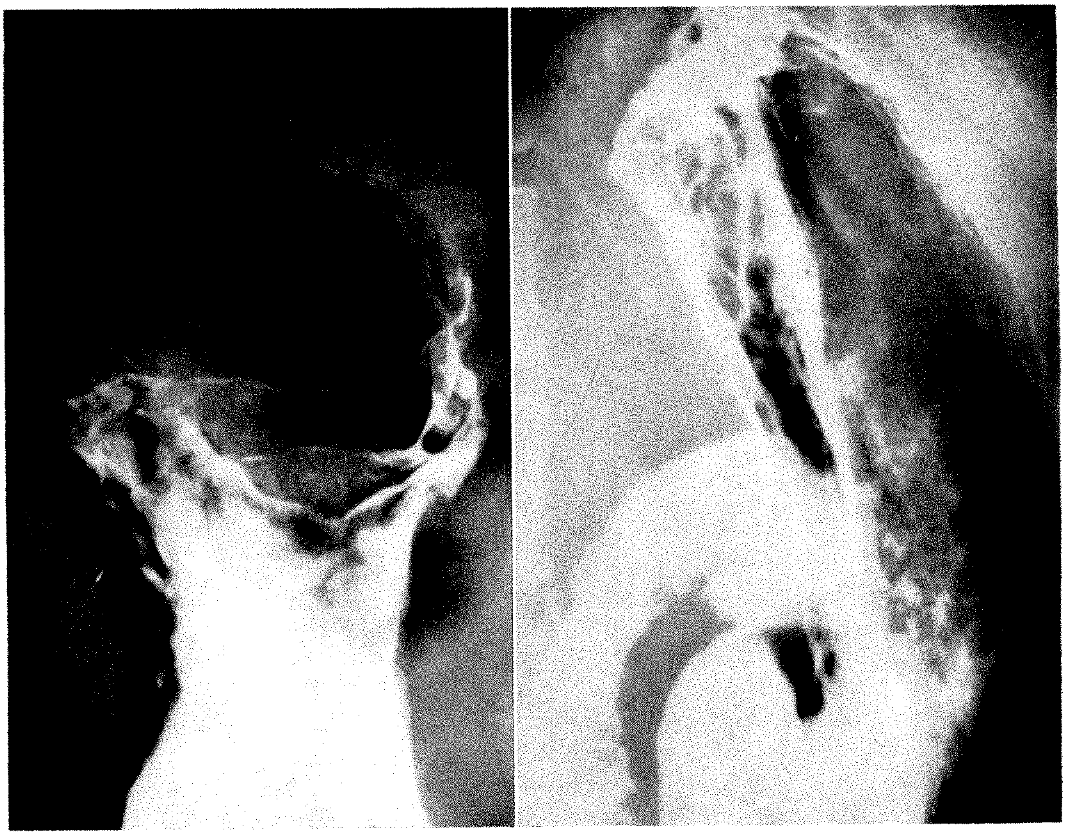
diagnostic problem. The differential diagnosis includes true neoplasia arising either from the mucosa or within the wall of the stomach, gastric varices, hiatus hernia, or the imprint of extrinsic masses (such as liver, spleen or kidney) on the stomach.

In a series of 40 patients with a radiological mass of the gastric cardia eight of the masses were not seen in repeat upper gastrointestinal series. These so-called "pseudotumors" were usually associated with a hiatus hernia and no intramural hematomas were reported in that series.[9] We agree with the suggestion that a repeat examination, preferably by gastroscopy, is essential in the diagnosis of all such cardia lesions. If, however, the lesion appears benign, it is valuable to allow a period of time (one week) between the initial and confirmatory examinations. The cases of intramural gastric hematomas reported thus far are summarized in Table I.

The present case was unusual in several ways. Firstly, the patient had been taking an anticoagulant, warfarin but had been doing so erratically. On admission her prothrombin time was 18.5 seconds but it may have been longer when her symptoms started three days before admission. Secondly, she had a circulating anticoagulant associated with her *S.L.E.* Thirdly, there was no history of any trauma which could have precipitated her cardia mass. Although we have no direct proof that this lesion was a hematoma, the transient and characteristic appearance on x-ray and on gastroscopy establishes with reasonable certainty that the lesion indeed was a hematoma.

Patients with *S.L.E.* may have gastrointestinal symptoms at some time in the course of their disease. Nausea, vomiting, diarrhea, abdominal pain and dysphagia are common and 5% of patients with these symptoms have gastrointestinal bleeding as a major complaint, mainly arising from small intestinal arteritis.[10] Although the clinical symptoms may often point to gastric involvement, histologically demonstrable disease of the stomach is an infrequent finding. Paulson[11] reported that of 72 cases of *S.L.E.* autopsied at Johns Hopkins Hospital, gastric arteritis was found in only three. No intramural hematomata of the gastrointestinal tract have been reported in *S.L.E.*

In the patient described, gastric biopsy specimens were inconclusive of the presence of arteritis but with the disease active as manifested by other signs and symptoms, we feel it reasonable to conclude that this was the underlying factor precipitating spontaneous hematoma while on warfarin. As has been shown in previous studies,[12] it is unlikely that the pres-



Figs. 3a and 3b—Repeat upper gastrointestinal series showing complete resolution of the cardia mass.

TABLE I

Reported Cases of Intramural Gastric Hematomata

| Case | Age | Sex | Position of hematoma | Underlying disease | Direct cause | Treatment |
|---|---|---|---|---|---|---|
| 1[4] | 8 | M | Posterior wall | Hemophilia A. | — | Frozen plasma |
| 2[5] | 27 | F | Fundus | ?Alcohol | Perforated gastric ulcer | Laparotomy |
| 3[5] | 48 | M | Fundus | — | Trauma from compressed air drill | Laparotomy |
| 4[6] | 41 | M | Antrum | Von Willebrands disease | Duodenal ulcer | Laparotomy |
| 5[6] | 8 | M | Greater curvature | Hemophilia A. | — | Antihemophilic globulin |
| 6[7] | 22 | M | Greater curvature | Hemophilia A. | — | Antihemophilic globulin |
| 7[8] | 72 | M | Cardia | — | Mallory-Weiss syndrome | Laparotomy |
| 8* | 24 | F | Cardia | *S.L.E.*<br>warfarin | — | None |

*Present case.

ence of a circulating anticoagulant in *S.L.E.* predisposes to bleeding.

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*Clinical Vignette*

# Surgical Treatment for *Pneumatosis Cystoides Intestinalis* Complicating Jejunoileal By-pass

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A case of chronic *pneumatosis cystoides intestinalis,* complicating jejunoileal by-pass procedure for morbid obesity, is described.

Grave clinical symptoms associated with irreversible segmental mucosal atrophy and mural fibrosis resulting from untreated long-standing *pneumatosis intestinalis,* required resection of the whole by-passed small intestine. It is suggested that this simple and safe surgical procedure is justified in selected cases. Conservative treatment of asymptomatic patients with *pneumatosis intestinalis,* however, may prevent further surgical intervention in these patients.

For the past 20 years intestinal by-pass procedures have been performed in cases of extreme obesity. Much work has been done in an attempt to define the indications, the operative technic and the complications of this procedure.[1, 2] Various surgical procedures have been planned among them a partial or complete reconstitution of the small intestine continuity[3-6] to overcome the grave complications of this operation.

This report presents the case of a patient suffering from *pneumatosis cystoides intestinalis* complicating jejunoileal by-pass and describes the associated irreversible pathological findings.

A hitherto unreported surgical solution to overcome the clinical complications, without depriving the patient of the beneficial effects of an adequate and irreversible weight loss, is presented.

## Case Report

A 44-year old nurse, gravida 2, para 4, was hospitalized several times in the course of 15 years in the Departments of Internal Medicine and Psychiatry for the investigation of extreme obesity. No endogenous abnormality was found and neither restricting diet nor pharmacological management overcame her obesity. In March, 1974 her height was 148 cm. and her weight, 105 kg. In order to relieve her obesity a Scott by-pass operation was performed anastomosing 36 cm. of jejunum end-to-end to 20 cm. of terminal ileum. The proximal cut end of the ileum was anastomosed end-to-side to the sigmoid colon. Postoperatively she suffered from diarrhea 15 times daily. At the end of the first month she was readmitted for treatment of an anal fissure, probably the result

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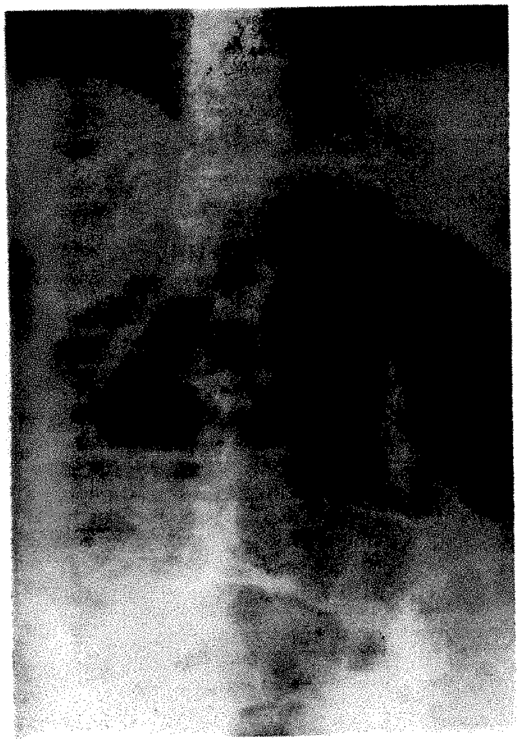

Fig. 1–Abdominal x-ray showing segments of dilated small and large intestine.

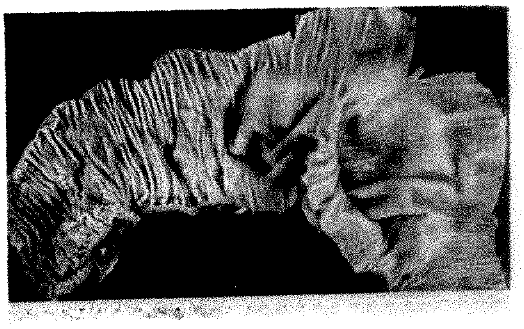

Fig. 2–Portion of the by-passed small intestine showing normal bowel alternating with an area of dilatation and complete loss of mucosal folds.

of continuous diarrhea. Six months later she was hospitalized again because of recurrent abdominal distention, nausea, vomiting and diarrhea. At that time, she weighed 80 kg.

Flat x-ray of the abdomen revealed several dilated loops of small intestine identified by barium enema to be in the by-passed small intestine. An upper gastrointestinal series revealed a normal esophagus, stomach and duodenum, with rapid transit (30 minutes) through the small intestine into the colon.

Conservative treatment relieved her symptoms. In May, 1975, more than a year after the Scott by-pass operation, she was hospitalized again and an emergency exploratory laparotomy was performed to free a volvulus of the by-passed loop, near the ileosigmoid anastomosis. No resection of the by-passed intestine was necessary. The functional jejunoileal segment was found to have lengthened the jejunum by 24 cm. and the ileum by 3 cm. Hence the functioning bowel was shortened to 58 cm. On the by-passed small bowel, as well as on its mesentery and on the descending colon, subserosal air cysts were noted typical of *pneumatosis cystoides intestinalis.* These changes were not present at the first operation. She tolerated the surgical procedure well but a week later laparotomy was performed because of small bowel obstruction caused by several adhesions which were then freed. Twenty-seven months after the initial operation she was hospitalized again, now weighing 78 kg.

She experienced recurrent attacks of abdominal pain associated with abdominal distention, nausea, vomiting and diarrhea. Abdominal x-rays during an attack revealed distended small and large intestinal segments (Fig. 1). This was interpreted as incomplete intestinal obstruction. Barium enema and upper gastrointestinal studies failed to demonstrate pathological findings responsible for the transient small bowel obstruction. Blood chemistry, electrocardiogram and pulmonary function tests were within normal limits. Colonoscopy done in search of a transient prolapse of the diverted small bowel into the sigmoid colon as described by Fikri[7] was negative. A

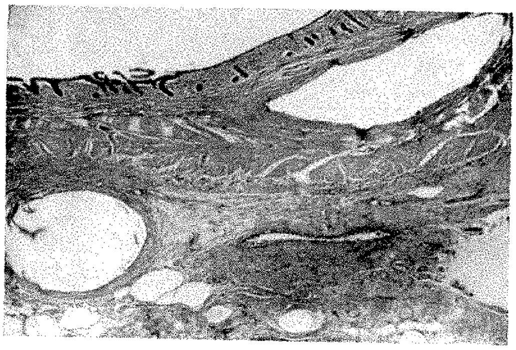

Fig. 3—Small bowel showing marked villous and mucosal atrophy, mural fibrosis and numerous submucosal and subserosal cysts (Hematoxylin and eosin, original magnification x28).

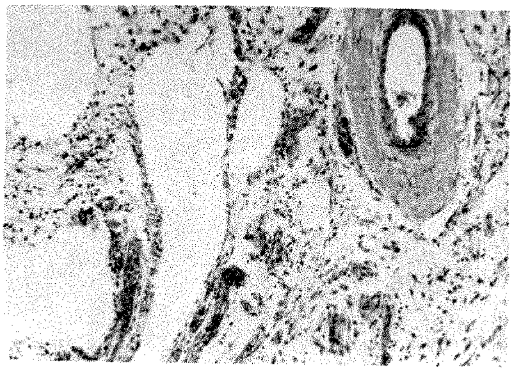

Fig. 4—Fibrous thickening of vessel wall adjacent to air-filled cysts in the intestinal wall (Hematoxylin and eosin, original magnification x250).

fourth laparotomy was then performed to ascertain the cause of the recurrent incomplete intestinal obstruction. Several adhesions were freed but no sign of compression was noted. The by-passed small intestine was extremely dilated although there were several skipped segments with a normal diameter. The descending colon was also dilated. Multiple subserosal air cysts, noticed in the previous laparotomy, were still present on the severely dilated and thickened areas of the by-passed small intestine.

These operative findings suggested an irreversible pathological state of the by-passed small intestine. Hence it was decided to resect the whole by-passed segment. She tolerated the surgical procedure well, recovered promptly and has had no further attacks of intestinal obstruction for a follow-up period of one year. Her weight has stabilized at 78 kg.; she has returned to work and is satisfied with her weight and physical condition. The resected segment showed areas of normal undilated intestine merging into areas of extreme luminal dilatation and complete disappearance of the mucosal folds (Fig. 2). Histologically the latter showed severe mucosal and villous atrophy and fibrous thickening of the intestinal wall (Fig. 3). This was mainly a reaction to the numerous submucosal and subserosal air blebs. No inflammatory changes were present in the intestinal mucosa. Most of the blood vessels in the involved area were surrounded by a thick mantle of fibrous tissue (Fig. 4). The villi and mucosa in the grossly normal area were within normal limits histologically.

## COMMENT

*Pneumatosis cystoides intestinalis* consists of a primary type in which the etiology is unknown and a secondary type associated with gastrointestinal pathology[8, 9] or a severe lung disease.[10, 11] Recently, several cases of coexistence of intestinal by-pass procedure and *pneumatosis cystoides intestinalis* have been reported,[12-14] thus adding a new complication to the widely recognized list of early and late complications of this surgical procedure.[2, 4, 6, 12, 13, 17-21] This combination ties up two possible mechanisms for the pathogenesis of *pneumatosis intestinalis*. Shortening the small bowel causes a long blind loop in which stasis, relative aperistalsis and diversion of bile acids cause ideal conditions for bacterial overgrowth and excess gas formation.[13, 18, 22] The proliferation of these bacteria forms the basis of *pneumatosis intestinalis*.[11, 23, 24] It is believed that these bacteria are responsible for the clinical symptoms of colonic pseudo-obstruction, lately described as "by-pass-entropathy".[13] Intestinal pseudo-obstruction and abdominal distention cause increased intraluminal pressure thus forming the mechanical element for *pneumatosis intestinalis*.[11, 15] It is further possible that the ileosigmoid anastomotic site also contributes to the formation of recurrent volvulus of the sigmoid or of the by-passed small intestine, thus increasing intraluminal pressure.[12, 16]

The clinical symptoms of *pneumatosis cystoides intestinalis* are similar to those of irritable colon, viz., abdominal distress meterorism, abdominal distention, diarrhea and sometimes, fever.[25, 26] These symptoms are similar to those described recently in "by-pass enteritis".[18] The cysts may also cause intestinal obstruction sometimes difficult to diagnose.[27]

Various treatments have been recommended to overcome the clinical symptoms attributed to the proliferation of bacteria in the by-passed intestine.[13, 18] Drastic relief has been achieved by revision of the intestinal by-pass procedure with restoration of the normal bowel continuity.[6, 13, 28] This, however, deprives the patient of the beneficial effects of weight-loss. Various treatments have been successfully used for *pneumatosis intestinalis*. Breathing of 70% oxygen for several days has produced collapse of the air-cysts.[29-31] Decompression of the small intestine via an Abbott-Miller tube or decompression of the rectum has been used in several other cases. When complications such as bleeding or intestinal obstruction occur, surgical removal of the involved bowel may be mandatory.[11, 12, 17, 25] The mere demonstration of *pneumatosis intestinalis* is ordinarily not an indication for conservative[32] or surgical treatment.[33] It has been widely accepted that there is no evidence that the asymptomatic form of this disease carries any substantial serious prognosis.[14, 25] Our patient, however, became symptomatic six months following the by-pass intestinal operation and six months later the existence of *pneumatosis intestinalis* was noticed during an exploratory laparotomy. Gradual deterioration followed the appearance of *pneumatosis intestinalis* similar to Meinhoff's patients with scleroderma of the small intestine.[34] Although the armamentarium of surgical procedures to overcome such conditions is well-known, it was decided on the basis of experimental[35] and clincial[4] knowledge to resect the whole by-passed segment. The severe atrophy and fibrosis of the intestinal wall[36] justified this procedure. A 12-month follow-up justified this decision.

This case raises some doubt concerning the benign course of *pneumatosis cystoides intestinalis* and demands a careful follow-up. We assume that in selected symptomatic cases, resection of the whole by-passed small intestine successfully accomplishes marked and safe symptomatic and curative relief.

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***Clinical Vignette***

# Metastatic Carcinoma Simulating *Linitis Plastica* of the Colon

## A CASE REPORT

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Reported herein is the case of a 70-year old woman with metastatic breast carcinoma presenting as *linitis plastica* of the ascending colon. The breast tumor was diagnosed nine years previously. The clinical, roentgenographic and pathologic features of colonic *linitis plastica* and the preoperative diagnostic difficulties are discussed. There is no difference in the morphologic features of primary and secondary *linitis plastica*. The latter may result from anaplastic carcinoma of the stomach, gallbladder or breast.

*Linitis plastica* refers to a diffusely infiltrating anaplastic carcinoma in a hollow organ, mainly of the gastrointestinal tract. The wall of the involved organ is usually rigid and somewhat thickened but its shape is maintained. Primary *linitis plastica* occurs most frequently in the stomach. In the colon, primary *linitis plastica* is rare; about 20 cases have been described.[1-11] The lesion is most often encountered secondary to metastatic carcinoma. The present communication describes the presentation of metastatic breast carcinoma as *linitis plastica* of the colon in a 70-year old woman.

## CLINICAL SUMMAY

A 70-year old woman was admitted to the hospital with a six-month history of weight loss, poor appetite and a two-month history of change of bowel habit. Past history revealed cholecystectomy 21 years and radical mastectomy for carcinoma of the breast nine years prior to admission. The only salient physical finding was a palpable mass in the right lower quadrant. There was no abdominal tenderness or distention.

At admission, the fasting blood glucose was 169 gm./dl.; hemoglobin, 11.4 gm./dl. and WBC, 12,700 with normal differential. The electrolytes, BUN and liver tests were within normal limits. The barium enema revealed numerous diverticula throughout the colon. The ascending colon, just above the cecum, showed a constriction defect which did not occlude the lumen. The postevacuation and air contrast studies confirmed the filling defect of the ascending colon. In conjunction with the clinical finding of a palpable mass in the right lower quadrant, the possibility of a malignant tumor was considered. The chest x-ray was negative for any discrete lesions. An intravenous pyelogram revealed a right obstructive

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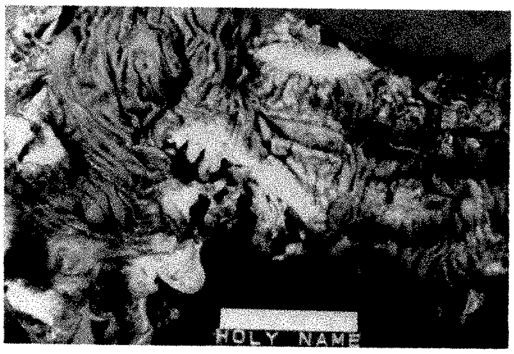

Fig. 1—Gross appearance of the colon showing thickening of the wall by grayish tumor and a coarsely granular appearance of the mucosa. The opening of a diverticulum is seen to the right of the specimen.

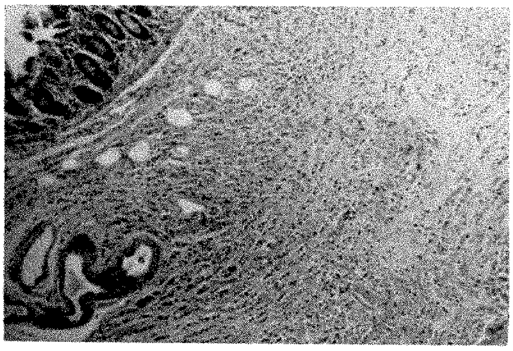

Fig. 2—Low power photomicrograph showing diffuse involvement of the colonic wall by anaplastic carcinoma. Note the absence of gland formation and relative sparing of the mucosa (Hematoxylin and eosin, original magnification x40).

uropathy at the ureteropelvic junction. Liver and spleen scans were unremarkable. At exploration, diffuse thickening and induration of large segments of small and large bowel with a discrete tumefaction of ascending colon was observed. The mesentery and the mesocolon was also extensively involved in the process. The stomach was free of any grossly recognizable lesions. No discrete lesions were seen in other abdominal viscera. A right hemicolectomy was performed to remove the large colonic mass. The surgeons were unable to distinguish this lesion from a diffusely inflammatory process such as granulomatous (Crohn's) ileocolitis. The postoperative course was uneventful.

## Pathological Findings

The specimen consisted of an ileocolic resection. The segments of the ileum and colon measured 15 and 39 cm. in length respectively. The mucosa, serosa and the wall of the small bowel were unremarkable on inspection but were indurated to palpation. The colonic segment showed a constricting lesion located about 12.5 cm. from the distal margin of resection. The lesion involved the entire circumference of the colon, measured 5 cm. along its length and was characterized by thickening of the wall and a coarsely granular appearance of the mucosa (Fig. 1). Irregular areas of thickening were found in other parts of the colon. Focal areas of normal-appearing mucosa were seen. Several diverticula were randomly distributed within the specimen. The pericolonic fat was thickened and sections showed infiltration by moderately firm grayish tissue. Numerous lymph nodes were present in the pericolonic fat.

Microscopically there was diffuse infiltration of the colon by anaplastic carcinoma, arranged mostly in single ("Indian") files (Figs. 2 and 3). The cells showed hyperchromatic nuclei and amphophilic cytoplasm. Some contained mucin, as demonstrated by mucicarmine and PAS stains ("signet ring" cells). Glandular formation was not seen in multiple sections. There was moderate to severe desmoplastic reaction. Perineural invasion was commonly seen. The lesion dissected through all layers of the colon but was most prominent in the submucosa and *muscularis*. There was focal mucosal involvement. Transition between normal colonic epithelium and the neoplasm could not be demonstrated. A review of the breast lesion removed nine

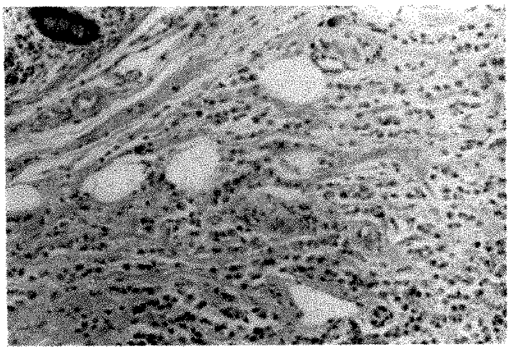

Fig. 3—Detail of anaplastic cells showing "Indian file" arrangement (characteristic of breast carcinoma) and moderate desmoplastic reaction (Hematoxylin and eosin, original magnification x100).

years previously showed morphologic similarity to the colonic tumor. Focal submucosal involvement of the small bowel was also present. Fifteen of 16 lymph nodes showed metastatic anaplastic carcinoma.

## COMMENT

*Linitis plastica* of the colon is rare, constituting about 1% of colorectal carcinoma.[12] While most cases are secondary to metastatic carcinoma, about a score of cases of primary *linitis plastica* of the colon have been described. The gross and histologic features in the present case are characteristic of this lesion. There are no pathological features that distinguish primary from secondary lesions. Grossly, the wall of the colon is moderately to severely thickened and rigid. A variable length of the bowel may be involved. The mucosal surface may be smooth without ulceration. The normal mucosal folds are absent and may be replaced by a coarsely nodular or granular appearance. Cut section demonstrates thin whitish streaks coursing through the thickened submucosa and *muscularis* at right angles to the length of the colon. By contrast to the observation that diverticula are not present in involved areas,[13] multiple diverticula with diverticulitis were admixed with the neoplasm in our patient. Microscopically, there is diffuse involvement of the colonic wall by anaplastic tumor cells, some of which may be mucin-secreting ("signet ring" cells). Moderate to severe desmoplastic reaction is the rule. Abortive glandular formation may be seen but is uncommon. By the time the patient presents, the tumor has extended to the pericolonic fat and metastatic carcinoma in the lymph nodes is usual, as was found in this case.

The roentgenographic diagnosis of colonic *linitis plastica* is most challenging.[9, 13, 14] The lesion, in its early stages, may be missed because of the absence of significant alterations in the configuration and motility of the colon.[13] With progression of the disease, however, there is narrowing and rigidity over a considerable length of the bowel. The mucosa is characteristically intact. Occasionally, however, an elevated or irregular mucosal pattern has been described. The margins of the lesion have tapered ends. Thus the lesion may simulate inflammatory lesions such as diverticulitis, ulcerative colitis, and granulomatous colitis or vascular lesions such as ischemic colitis.[9] The absence of an intraluminal mass or features of annular carcinoma compounds the diagnostic difficulties. In the present case, a preoperative suggestion of malignancy was made on the radiologic appearance of the colon and the presence of a palpable mass in the right lower quadrant.

The diagnosis of primary *linitis plastica* of the colon can be made only in the absence of a carcinoma with a similar histological appearance in other parts of the body. The majority of the *linitis plastica* of the colon are secondary to metastatic carcinoma, most often from a gastric primary.[15-17] Rarely, the primary tumor may be an anaplastic carcinoma of the gallbladder.[18] The literature contains five cases of *linitis plastica* of the colon secondary to metastatic breast carcinoma.[15, 17, 19, 20] In all the cases there was either a simultaneous discovery of breast carcinoma with disseminated metastases, of which the colonic component showed *linitis plastica* pattern, or the colonic lesion was diagnosed months to years after the breast carcinoma. In the present case, breast carcinoma was diagnosed nine years before the discovery of the colonic lesion. It is interesting that metastatic carcinoma was not encountered in any other organ.

Wide excision of the lesion has been proposed because of the difficulty in ascertaining the extent of the disease at surgery, even with the aid of frozen sections. Additionally, it has been recommended that women should undergo hysterosalpingo-oophorectomy because of the tendency for early involvement of the ovaries.[7, 9] Although the prognosis is uniformly poor because of the insidious nature of the tumor and the high percentage of lymphatic dissemination at the time of diagnosis, the use of chemotherapeutic agents as adjunct to surgical therapy may improve the survival rate.

## ACKNOWLEDGMENT

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# State of the Art*

## MANAGEMENT OF PATIENTS WITH POLYPOID LESIONS OF THE COLON—CURRENT CONCEPTS AND CONTROVERSIES

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The title for this review was chosen deliberately in an attempt to emphasize and clarify certain controversies which currently exist in relation to polypoid lesions of the colon. A polypoid lesion of the colon is any negative filling defect seen on barium enema or any mass seen to be protruding into the lumen of the colon at the time of colonoscopy. It is a clinical definition that avoids the term "polyp" which has certain histologic implications which may not be grossly apparent to the endoscopist or radiologist at the time of their examination. The gross appearance of a lesion may suggest a pathologic etiology but a specific histologic diagnosis must be obtained by excision or biopsy of all such lesions.

Definition of the number and location of polyps is desirable. "Single" or "solitary" is self-explanatory. The differentiation of "multiple" from "diffuse" is a little more difficult. "Multiple" is the presence of two or more lesions. These may range from numerous lesions located in one region of the colon up to approximately ten lesions scattered throughout the colon from the anus to the cecum. For example, if there were ten lesions in the sigmoid colon, I would employ the term "multiple polyps of the sigmoid colon". If, however, there were ten lesions scattered from rectum to cecum, I would use the term "diffuse polyps of the colon". At some point the definitions merge but the exact point is arbitrary, debatable and of dubious value. "Familial polyposis" and related syndromes refer to distinct clinical and pathologic entities where the colon is carpeted by hundreds of polypoid lesions.

The pathologist makes the definitive microscopic diagnosis of a polypoid lesion and thus aids us in planning the future management of the patient. Although there is some disagreement concerning histological classification of polypoid lesions of the colon, the following classification reflects current concepts:[1] 1. tubular adenoma (adenomatous polyp); 2. villous adenoma; 3. tubulo-villous adenoma (mixed, intermediate, villoglandular); 4. hyperplastic; 5. inflammatory; 6. juvenile; 7. sessile mammilation (mucosal excrescence); 8. polypoid adenocarcinoma; 9. miscellaneous and rare lesions: Peutz-Jeghers syndrome, lipoma, fibroma, leiomyoma, leiomyosarcoma, carcinoid, endometrioma, lymphoma, angioma, neurofibroma, lymphangioma, myoblastoma, melanoma, rhabdosarcoma, plasmacytoma, colitis *cystica profunda* and the Canada-Cronkite syndrome.

The pathologic definition of each lesion is beyond the scope of this paper. Certain principles must be emphasized, however, because they will affect the management of the patient.

A sessile mammilation (mucosal excrescence) by common usage, is any lesion 3 mm. or less that is flat, usually diagnosed only at colonoscopy which is being done for some other reason and is not seen on

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TABLE I

RELATIONSHIP OF SIZE AND HISTOLOGY TO % CANCER

| | % CA | Size and % CA | | |
|---|---|---|---|---|
| Histological type | | 1 cm. | 1-2 cm. | 2 cm. |
| Tubular adenoma | 4.8 | 1.0 | 10.2 | 34.7 |
| Tubulo-villous adenoma | 22.5 | 3.9 | 7.4 | 45.8 |
| Villous adenoma | 40.7 | 9.5 | 10.3 | 52.9 |

* Modified from Muto, et al.[9]

TABLE II

RELATIONSHIP OF SIZE AND OCCURRENCE OF ADENOMAS TO % CANCER

| Size | Occurrence | % CA |
|---|---|---|
| 1 cm | 59.4 | 1.3 |
| 1-2 cm. | 23.3 | 9.5 |
| 2 cm. | 17.3 | 46.0 |

* Modified from Muto, et al.[9]

x-ray, even a double contrast barium air enema.[1] Over 95% of these lesions are hyperplastic and do not represent true neoplasia.[1-3]

Polypoid lesions of the colon should be removed for two reasons: First, certain ones may have malignant potential or are already frankly malignant. Second, some are symptomatic regardless of histology, (bleeding, intussusception, change in bowel habits). It was formerly believed that the relationship between colon polyps and colon cancer was either nonexistent or rare and that most carcinomas arose *de novo*.[4-6] The evidence accumulated over the past decade appears to strongly refute this idea. It is highly probable that most carcinomas of the colon arise from benign adenomas and there is a definite benign adenoma-carcinoma sequence.[7-9] There are excellent long-term pathologic observations which show a definite correlation between the malignant potential of benign adenomas and their microscopic character, size and number.[9]

Approximately 75% of all colon adenomas are tubular, 15% tubulo-villous, and 10% villous.[9] Atypia and dysplasia may be precursors but are not carcinoma.[9] Carcinoma *in-situ,* that is carcinoma which has not penetrated the *muscularis mucosa,* is a pathologic but not a biologic cancer.[9] No case of metastasis has been reported in such a case.[10] Tables I and II contain statistics related to carcinoma which has penetrated the *muscularis mucosa.*

Several conclusions may be drawn from reviewing these statistics. Most polypoid lesions are tubular in nature, under 1 cm. in diameter and have a small but definite risk of malignancy. Tubular adenomas tend to be the smallest lesions and villous adenomas, the largest. All polypoid lesions, however, have the potentiality to enlarge and the larger they become, the greater the incidence of malignant change. It would seem that although both factors are significant, size is more influential than histologic type in predicting the presence of carcinoma in any particular lesion. Atypism is correlated with a significantly greater occurrence of carcinoma in growths 1 cm. or less and thus is of most importance in tubulo-adenomas; somewhat related in lesions 1-2 cm. in size and has no significance in adenomas over 2 cm. in size.[9] Severe atypia in a polyp is associated with an increased risk of carcinoma occurring in other areas of the colon.[11]

Twenty per cent of all patients with colon tumors have more than one (synchronous) growth in their colon when they are first seen; about 10% develop a new growth (metachronous lesion) later.[9, 10] The greater the number of adenomas present, the greater the risk of carcinoma, either synchronous or metachronous.[12, 13]

It would appear that if we have a method of easily, safely and economically removing adenomas of the colon, a great forward stride in the prevention of carcinoma of the colon could be achieved. A prospective double-blind clinical trial would give us the ultimate answer. Such a study at this point, however, is probably unethical and perhaps unnecessary.

There are a number of retrospective studies which are relevant to this question. Gilbertsen has shown that removal of all rectosigmoid adenomas visualized through a sigmoidoscope in a group of 18,000 patients over a period of 25 years decreased the incidence of localized cancers in that region of the colon by 86%[14] Two other studies seem to support this conclusion. In a 15-year followup of patients with adenomatous polyps removed at sigmoidoscopy the risk of colon cancer was twice that expected in a normal population.[3] A Swedish study found that 7% of patients free of polyps developed polyps after eight or more years of observation and none developed carcinoma. In a similar number of patients who did have polyps on initial examination, 21% developed new polyps and 2.7% developed carcinomas over approximately the same observation period.[11]

Another study reviewed the course of 154 patients with colon polyps who were followed for a mean of seven years.[15] Over all, 30% of patients developed recurrent polyps. The risk was 16 times greater than in a normal population for the first year but diminished with time so that after four years the risk was only slightly higher than the normal population. One third of patients with one recurrence developed a second recurrence and although numbers were small, this subgroup seemed to develop further polyps with time. Four patients developed carcinoma. Patients with villous adenomas had a higher recurrence risk. The greater the number of polyps removed at the initial examination, the greater the recurrence rate (Table III).

TABLE III

EFFECT OF NUMBER OF POLYPS EXCISED ON SUBSEQUENT POLYP RECURRENCE[15]

| No. polyps removed | No. patients | % recurrence |
|---|---|---|
| 1 | 82 | 28 |
| 2 | 10 | 41 |
| 3 | 2 | 60 |
| 3 | 2 | 80 |

The first major problem encountered is the ability to diagnose polyps. Most polyps are asymptomatic except for the few that produce overt bleeding, or pain via intussusception. Once a polyp becomes symptomatic, there is a greater likelihood that it has become malignant. At the present time, the majority of colon polyps are discovered during a barium enema done as part of a routine work-up or becauhe of overt or occult gastrointestinal bleeding with or without anemia, abdominal pain, change in bowel habits or significant pathology discovered at sigmoidoscopy. Recent screening with the Hemoccult test has also resulted in an increased diagnostic rate of early neoplastic lesions of the colon.[16] It is still probably true, however, that the majority of colon polyps remain undetected in their early development. Hemoccult testing, sigmoidoscopy and a good air contrast barium enema at present are the most practical initial screening procedures for colon polyps.

The incidence of carcinoma of the colon has been steadily rising and there are approximately 100,000 new cases each year.[17] Earlier diagnosis is extremely worthwhile because there is a 67% ten-year survival rate if colon cancer is localized, whereas there is only a 30% ten-year survival rate if it is not. If the lesion is asymptomatic, there is a 90% five-year survival rate. Since only 10% of all adenomatous polyps become malignant, the implication is that the incidence of adenomatous polyps approaches one million per year. Accounting for the fact that there is an average of 1.5 polyps per patient, there may be over 650,000 new patients per year with adenomatous polyps. Adenomatous polyps account for only 10% of all polypoid lesions of the colon and another 1% may be in the category of a rare lesion. This means that there may be as many as seven million new patients per year with all types of polypoid lesions of the colon. If one assumes that 50 million people are under the age of 20 and therefore less likely to have polyps, then roughly one adult in 28 may have a polypoid lesion of the colon. If there are only 3,000 physicians in the country performing colonoscopy, and seven million patients might benefit by the procedure, one is left with the figure that each colonoscopist would have to do 2,333 colonoscopies per year.

My figures are not exact, but I have engaged in this statistical frivolity in order to emphasize the enormous logistical problems that exist. There are not enough physicians, time, or money to perform adequate x-ray and endoscopic examinations on all these potential patients.

Therefore, we must try and identify those groups of patients who may be at higher risk to develop adenomas and carcinoma of the colon (Table IV).

TABLE IV

RISK FACTORS IN COLORECTAL CANCER[16]

*Age:*—Over 40 in asymptomatic males and females.

*Associated disease:*—Ulcerative colitis, granulomatous colitis, Peutz-Jeghers, familial polyposis.

*Past history:*—Colon carcinoma or polyp; female genital or breast cancer.

*Family history:*—Juvenile polyp, carcinoma of the colon, colon polyp, familial polyposis.

This selection process begins to reduce the number of patients at risk to a practical number and to match our capability to achieve earlier diagnosis and treatment and improve survival in the patients who are at highest risk. The largest, least selective group of patients are those over the age of 40. This group can be further reduced by employing the Hemoccult screening test and examining only those with a positive result. It has had an excellent correlation with significant colon pathology. There is a 1% false positive rate, false negatives are 0.03% for carcinoma, 0.24% for polyps over 5 mm. and 0.49% for polyps under 5 mm.[16]

The use of serum CEA levels as a further screening procedure at this time is probably not helpful. There is some evidence that patients with colon adenomas and increased levels of serum CEA may be at higher risk for development of carcinoma and that CEA is more likely to be increased in patients with villous adenomas or adenomas over 2-3 cm. in diameter.[18] Analysis of CEA in colon lavage fluid showed increased amounts of CEA in patients with polyps over 1 cm. and also in patients with carcinoma. Serum CEA levels were normal in these patients except in two individuals who already had metastatic cancer.[19]

Should these high risk patients undergo barium enema, colonoscopy or both as the initial diagnostic procedure to increase the diagnostic yield of colon polyps and thus improve the chance of preventing or curing colon cancer?,

The ideal study to determine the relative accuracy of colonoscopy and barium enema in diagnosing polypoid lesions of the colon has not yet been done.[20] Several reports in the past two years, however, have shed some light on this dilemma. Williams reported that of patients undergoing colonoscopy and polypectomy, 98% of polyps over 1 cm. and 78% of polyps under 1 cm. had been previously diagnosed by double contrast barium air enema. Seven per cent of lesions diagnosed by double contrast barium air enema were not substantiated at colonoscopy. Standard barium enema, however, detected just 77% of polyps over 1 cm. and only 18% of polyps under 1 cm. in diameter.[21, 22] Wolff, in a similar retrospective review, found only 58% of polyps had been diagnosed on routine barium enema prior to colonoscopy ranging from 27% of polyps under 1 cm. to 92% of polyps over 2 cm.[23] Laufer's study showed a 17% false negative colonoscopy and a 10% x-ray false positive double contrast barium air enema.[24] In his study it is pertinent to note that colonoscopy did not diagnose any polyps not previously seen by double contrast barium air enema and x-ray was used as the standard by which colonoscopy success was determined. This study also did not show a breakdown as to polyp size and is at variance with all the other studies. A major reason for the variance may be that their total colonoscopy experience was limited to just 150 cases at the time this report was published. The main theme of the paper and the major implication to be drawn from it, however, which I think is true, is that colonoscopy misses polyps, particularly under 1 cm. in size in certain regions of the colon where the polyps are likely to be behind haustras or at points of acute angulation of the colon. Another study showed that routine barium enema had a 45% false negative rate while double contrast barium air enema had only an 11.7% false negative rate. Colonoscopy missed 2.7% of radiologically diagnosed polyps.[25]

It is clear that the yield of double-contrast barium air enema is significantly higher than standard barium enema in diagnosing colon polyps, particularly under 1 cm. in size. Double contrast barium air enema still misses about 20% of polyps less than 1 cm. in diameter and colonoscopy is much more accurate in finding lesions between 0 and 10 mm. It would seem that, in experienced hands, colonoscopy misses about 2-5% of colon polyps. Certain areas of the colon are better seen on double contrast barium air enema and others at colonoscopy. The two methods are diagnostically complementary. Therefore, I would suggest utilizing both double contrast barium air enema and colonoscopy in initial workup for patients with suspected colon polyps. The use of both procedures in high risk patient groups should result in the highest possible diagnostic rate of colon polyps.

Preoperative colonoscopy is indicated in patients undergoing colon resection for carcinoma in order to discover and possibly remove synchronous lesions.[26] The findings at colonoscopy may alter the surgical approach. If obstruction prevents total colonoscopy, postoperative colonoscopy should be carried out as soon as possible.

Experience gained over the past decade has shown that most polyps visualized during colonoscopy can be completely removed by cautery snare.[27-30] The safety of the procedure has been substantiated by the low incidence of complications, morbidity 0.22-0.8%, mortality 0.008%-0.026%, reported in numerous series.[31-35] Hemorrhage occurs in 0.2-4%, is immediately apparent in 90%, delayed in 10%, rarely requires transfusions (20%) and even more rarely requires surgical intervention (5%). It usually ceases spontaneously, sometimes can be stopped by application of adrenalin or resnaring and recoagulating the stalk, or by intravenous or intra-arterial infusion of pitressin. Perforation occurs in

0.22%-0.66%. Sixty-five per cent of all perforations require surgery. Perforation due to manipulation is more serious and usually requires prompt surgical treatment (79%). Perforation due to electrocoagulation may be delayed and in many instances, especially if there is little or no free air seen on abdominal x-rays, is minor enough so that it can be treated conservatively with antibiotics, keeping the patient off all oral intake and providing intravenous fluid and electrolyte maintenance (46%). Serosal tears and transmucosal burns present with pain, fever, and leucocytosis without free air and can usually be managed in the same fashion and the patients will become asymptomatic in 48-72 hours. Complications decrease as the colonoscopist gains experience.

Morbidity, mortality and costs are significantly less than polypectomy by laparotomy which is justified only when an experienced endoscopist has decided that endoscopic polypectomy is not possible.[36-38]

Malignant changes in polyps are frequently missed by single and even multiple forceps biopsies, therefore, histologic evaluation should be based on examination of the completely excised polyp.[39]

I believe all lesions over 0.5 cm., except for lipomas which are usually grossly identifiable, should be totally removed to ascertain histologic type and provide guidance for definitive therapy. This statement must be tempered by the physician's clinical judgment regarding a patient's age, risk group and presence of other serious diseases. The 0.5 cm. figure is used because it encompasses virtually all adenomas reported to have shown malignant change.

The management of lesions under 0.5 cm. is more controversial. Most of these lesions are discovered at the time colonoscopy is being done for other reasons. If there are less than ten such lesions and they are 0.3-0.5 cm. in diameter. I would carry out hot biopsy forceps fulguration. If they are 1-2 mm. in diameter I would eradicate them by fulguration if there are ten or less. If there are more than ten lesions of this size, I would not try to destroy all of them, but might biopsy a few for representative histologic diagnosis. I realize these decisions are arbitrary. They are arrived at on both a practical and a logical basis. Only 10% of the small lesions are truly adenomatous, the rest are hyperplastic and are not considered to have neoplastic potential. The incidence of carcinoma occurring in a lesion under 0.5 cm. is at most one in 200. Therefore, one would have to remove and/or destroy 2,000 lesions under 0.5 cm. to cure one small carcinoma. Furthermore, most of these patients will be put into a one-year follow-up group because another larger lesion was removed at the same time. It has been estimated that the growth rate of colon carcinoma is approximately a doubling in size in 180-300 days, therefore, the enlargement of a neoplastic or potentially neoplastic lesion should be obvious on follow-up examination in one year and the lesion should still be small enough so that it can be totally removed and effectively cured.[40, 41] It is also known that some of these small sessile mammilations regress, although, the mechanism is unknown.

Postpolypectomy follow-up of patients depends on a variety of factors. If feasible, total colonoscopy should be attempted at the time of initial polypectomy.[42] In a small number of patients, this is not possible for a variety of reasons, (time spent removing a large lesion, multiple lesions, possible complications such as bleeding), in which case total colonoscopy should be carried out a few weeks later.

Patients who have a solitary benign polyp 1 cm. or smaller removed should undergo repeat double contrast barium air enema in 12 months. I cannot argue on a scientific basis with anyone who would want to make the repeat examination a colonoscopy but I believe an argument can be made on a cost-effective basis. This group of patients is at least risk and it has been suggested previously that double contrast barium air enema is almost as good at picking up lesions over 1 cm. as colonoscopy and it is much less expensive. On the other hand, it would be very difficult to argue with the proposal that this group of patients should have double contrast barium air enema at six months and colonoscopy at 12 months or undergo both examinations at the end of one year since the methods are diagnostically complementary. One might also argue that if colonoscopy missed a synchronous lesion the first time it was done, why is there any reason to think that it would be more accurate the second time.[7] Until such time as planned prospective studies show the relative merits of the ability of double contrast barium air enema versus colonoscopy to diagnose synchronous colon polyps, I believe it best at the present time to perform both a double contrast barium air enema and a colonoscopy at the time of the one year follow-up. The reason for emphasizing the one-year postpolypectomy examination is that it improves chances of finding a synchronous polyp missed at the time the original lesion was removed. If the examination is negative after one year, these patients should probly then enter the polyp-cancer surveillance screening described subsequently for multiple or larger solitary polyps.

Patients with multiple benign polyps or a solitary benign polyp larger than 1 cm. warrant both follow-up colonoscopy and double contrast barium air enema in 12 months to search for synchronous polyps not seen at the initial examination because they are subject to increased risk of malignancy. If the first follow-up examination is negative, repeat examination is indicated in three years. Interval Hemoccult testing should be done yearly and all patients with positive tests examined by double contrast barium air enema and colonoscopy. Follow-up should probably be by double contrast barium air enema alone in those patients in whom total colonoscopy is technically difficult. If a polypoid lesion is found, a decision must then be made as to the feasibility of endoscopic removal. The remainder of this group of patients should have colonoscopic follow-up in three years. If a polyp or polyps are found, they are removed and the patient then re-enters the follow-up program one year later.

What should we do with these groups of patients when follow-up examinations are negative one year and three years postpolypectomy? What little evidence there is suggests that the risk of recurrence in those patients with one polyp after one year is extremely small.[15] This would suggest that these patients should re-enter the normal population group which is followed by yearly Hemoccult testing. I do not think, however, there are enough data yet to justify this and suggest continuing on a three-year follow-up schedule until such data are available. Patients with two or more polyps seem to be at increased risk past four years (although numbers are very small). Therefore, I would definitely continue their surveillance every three years.

Patients with adenomatous polyps exhibiting carcinoma superficial to the *muscularis mucosa* can be followed in the same manner as patients with benign polyps.

The management of patients with pedunculated polyps exhibiting carcinoma extending beyond the *muscularis mucosa* is controversial.[10, 43-45] Colonic resection is probably not necessary if invasion of the carcinoma is confined to the distal head of the polyp, is highly differentiated, has not invaded the lymphatics or blood vessels and is not present in the neck of the polyp. There should probably be at least 6 mm. of normal stalk remaining. No lymph node metastases have been found when the above criteria were met. Positive lymph nodes have been found in about 10% of patients when these criteria are not adhered to and surgical resection is advised in this group of patients. The physician's clinical judgment is most important in assessing the relative risk of mortality from surgery in such patients versus the probability of lymph node metastasis already being present which might be cured surgically. Colonoscopic examination of the polypectomy site should be repeated three to six months later and again at one year. If re-examination is normal after one year, the patient enters the three-year re-examination cycle. If a lesion is observed at three to six months, it is cautery snared. If it is just normal tissue (postpolypectomy deformity) the patient enters the three-year re-examination cycle. If adenomatous tissue is removed, re-examination is carried out again three to six months later. Surgical resection is indicated if malignant tissue is found.

Good surgical risk patients with a sessile polyp exhibiting carcinoma that has penetrated the *muscularis mucosa* should undergo surgical resection. Colonoscopic excision may have to suffice as adequate treatment in extremely poor risk surgical patients.

The malignant potential of villous adenomas is quite significant; therefore, patients undergoing colonoscopic excision of villous adenomas should have repeat colonoscopy at two to four months and again at 12 months to document complete removal and to insure against recurrence. They should probably be re-examined yearly until they have been shown to be free of tumor for three years and then can enter a three-year follow-up program.

Although areas of controversy still exist concerning the management of patients with single or multiple polypoid lesions of the colon, I think that these current concepts provide an adequate basis for rational care of these patients. They also indicate those deficient areas where we must gather further data in a controlled manner to resolve the remaining controversies.

Perhaps some statement of opinion is needed concerning problems of a national scope. Our goal is to eradicate or at least decrease the prevalence of colon cancer and its sequels. We appear to have the methods for doing this, however, there are too few physicians adequately trained in colonoscopy and perhaps even the method of performing an accurate double contrast barium air enema. The training of physicians and purchase of equipment is very costly. In this era of "little is better" we will achieve our goal only by increasing the number of physicians participating in the diagnosis and treatment of colon lesions and improving the efficiency of both the physicians and the procedures they are performing. We must also raise the level of the standards of training and practice. The distribution of endoscopists must be more geographically balanced or a system of regional referral centers must be established. All of this must be implemented while costs are contained. The task is difficult but within our capability to solve.

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# The Radiology Corner*

## EMPHYSEMATOUS CHOLECYSTITIS†

HAROLD JACOB, M.D.
ROBERT APPELMAN, M.D.
and
H. DAVID STEIN, M.D.
Bronx, NY

The radiographic spectrum of emphysematous cholecystitis can be divided into three stages. Diagnosis on plain abdominal film is difficult in the first stage. Two cases are presented in which a circular gas filled structure in the right upper quadrant led to a correct diagnosis in the earliest stage. This was confirmed by obtaining contrast studies to rule out other etiologies.

The presence of gas in the gallbladder was first discovered at autopsy by Stolz in 1901[1] and described at surgery by Lobinger seven years later.[2] Hegner was the first to make the diagnosis of emphysematous cholecystitis preoperatively in 1931 on the basis of roentgenograms.[3] The two cases reported here demonstrated gas in the lumen of the gallbladder which is the first stage in the roentgenographic spectrum of emphysematous cholecystitis. A ring of gas is present within the gallbladder wall in the second stage. In the third stage, gas is seen in the pericholecystic tissues.[4]

### CASE REPORTS

*Case 1:*—A 70-year old male was admitted with a four-day history of generalized abdominal pain more pronounced in the right upper quadrant. There was no history of diabetes mellitus, alcohol abuse, or prior episodes suggestive of biliary tract disease. Vital signs were stable with a temperature of 37.5° C. There was guarding and tenderness in the epigastrium and right upper quadrant. The WBC count was 8,300/cu. mm. A plain film of the abdomen revealed a circular lucency in the right upper quadrant, felt to be gas in the lumen of the gallbladder or a dilated duodenal bulb (Fig. 1). A Gastrografin study revealed that the lucency noted was not related to the intestinal lumen (Fig. 2) Twelve hours after admission the patient became toxic with a temperature of 38.7° C and WBC count of 16,900/cu. mm. Upright films of the abdomen showed that there was an air fluid level at the site of the previously noted lucency. The patient was taken to the operating room with a presumptive diagnosis of emphysematous cholecystitis. During induction of anesthesia, the right upper quadrant mass became clearly visible as shown in Figure 3. An acutely inflamed gallbladder, which was markedly distended with gas, was demonstrated at surgery and a cholecystectomy was performed. Anaerobic culture of the gallbladder grew *Clostridium perfringens* and the patient was treated with appropriate antibiotics. The pathologic specimen showed the cystic

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* Edited by Richard H. Marshak, M.D., F.A.C.G. and Arthur E. Lindner, M.D., F.A.C.G.

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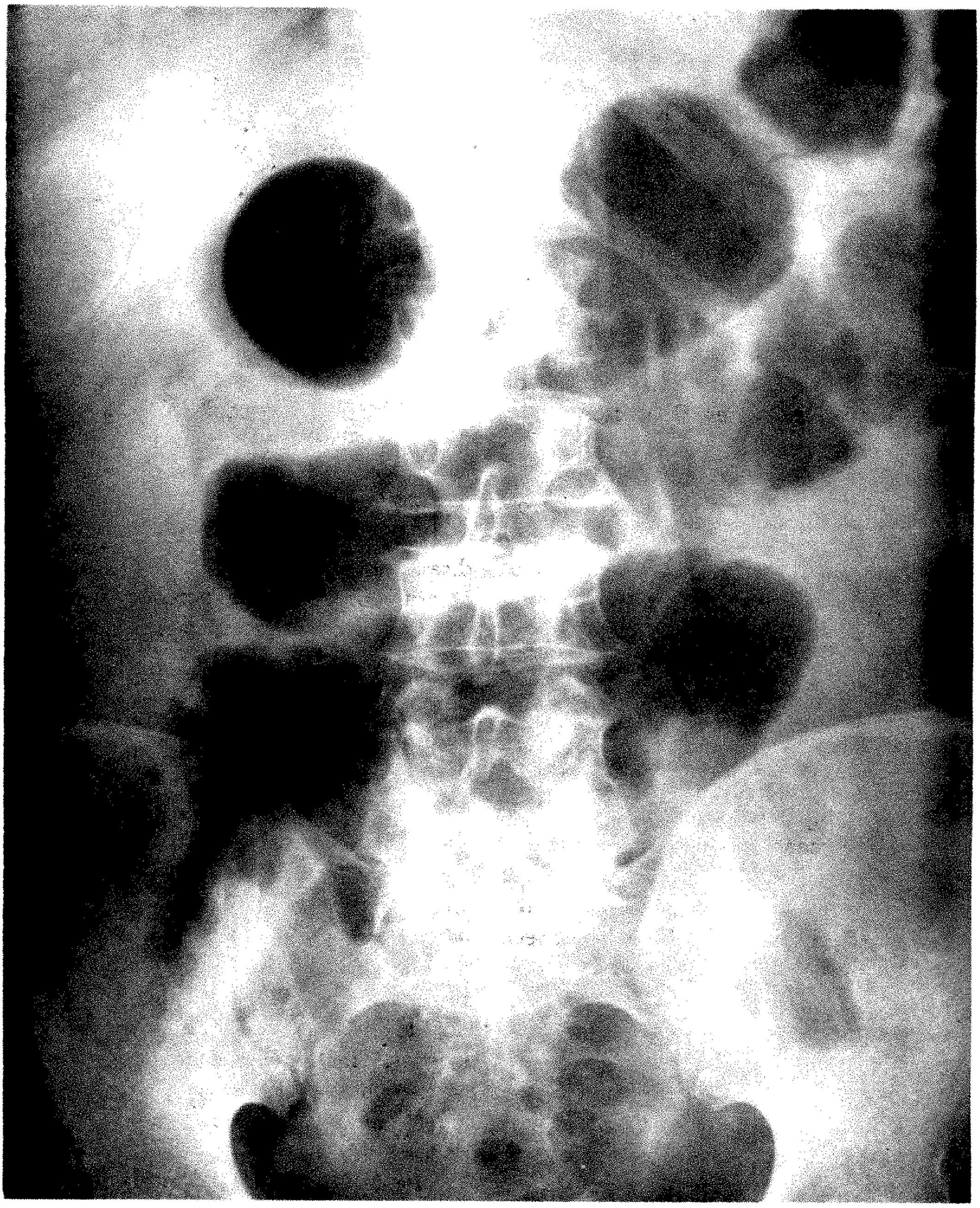

Fig. 1—Plain film of the abdomen revealing a circular lucency in the right upper quadrant.

duct to be occluded by thick inspissated bile and there were no stones present. The patient's postoperative course was uncomplicated.

*Case 2:*—An 85-year old male was admitted to the hospital because of progressive abdominal distention with generalized abdominal pain of one week's duration.

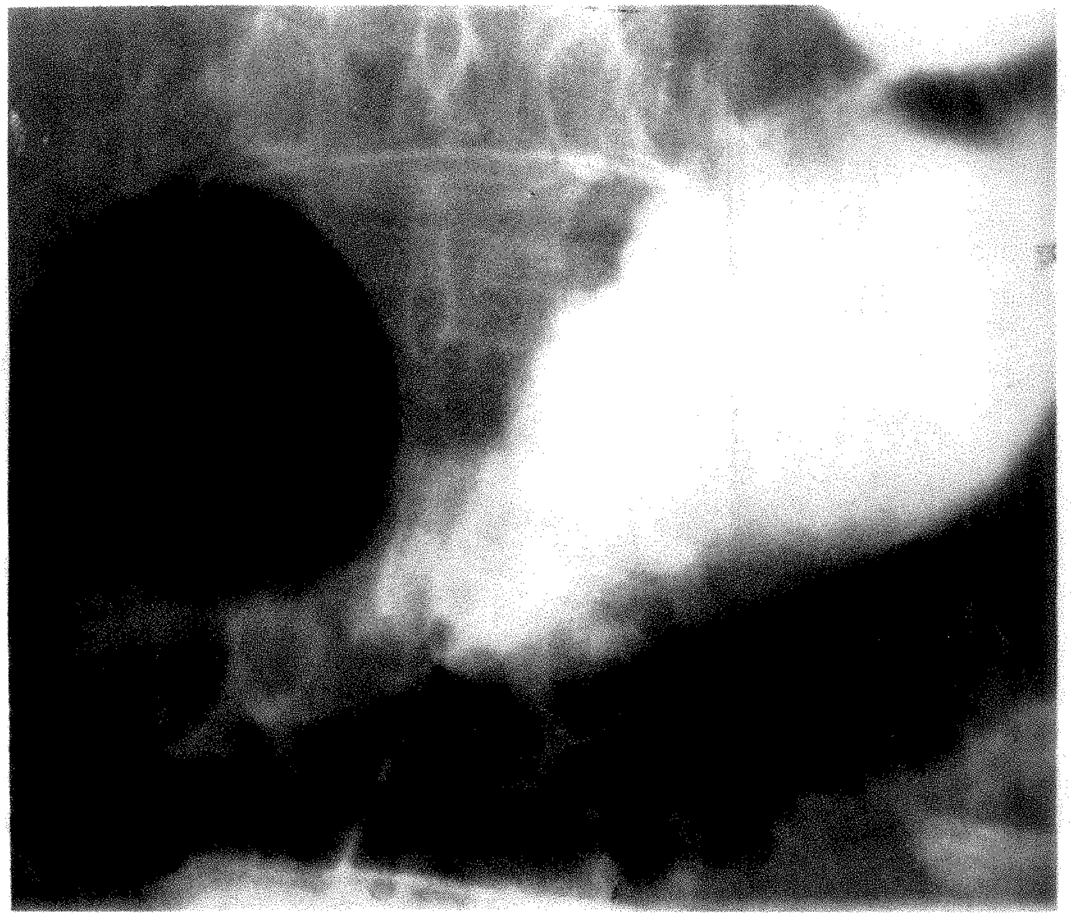

Fig. 2—Gastrografin study shows that the lucency was not related to the upper gastrointestinal tract.

There was a past history of diverticulosis but he denied diabetes mellitus, alcohol abuse, or prior episodes suggestive of biliary tract disease. The patient had a fever of 38° C. The remainder of the vital signs were stable. The abdomen was distended with generalized tenderness noted. There were no palpable masses present. The WBC was 17,600/cu. mm. Abdominal plain films revealed an ileus pattern of the bowel with a right upper quadrant round lucency. A Gastrografin study showed that this was unrelated to the upper gastrointestinal tract and a barium enema showed the lucency to be unrelated to the lower gastrointestinal tract (Fig. 4). The diagnosis of emphysematous cholecystitis was made. The patient refused surgery and became asymptomatic on antibiotic therapy. He was discharged feeling well, only to return two weeks later with signs of an acute abdomen. A preoperative diagnosis of emphysematous cholecystitis leading to perforation of the gallbladder was made and a cholecystectomy was performed. Anaerobic culture of the gallbladder grew *Clostridium perfringens*. The pathologic specimen demonstrated a gangrenous gallbladder with no evidence of gallstones. The patient did well postoperatively.

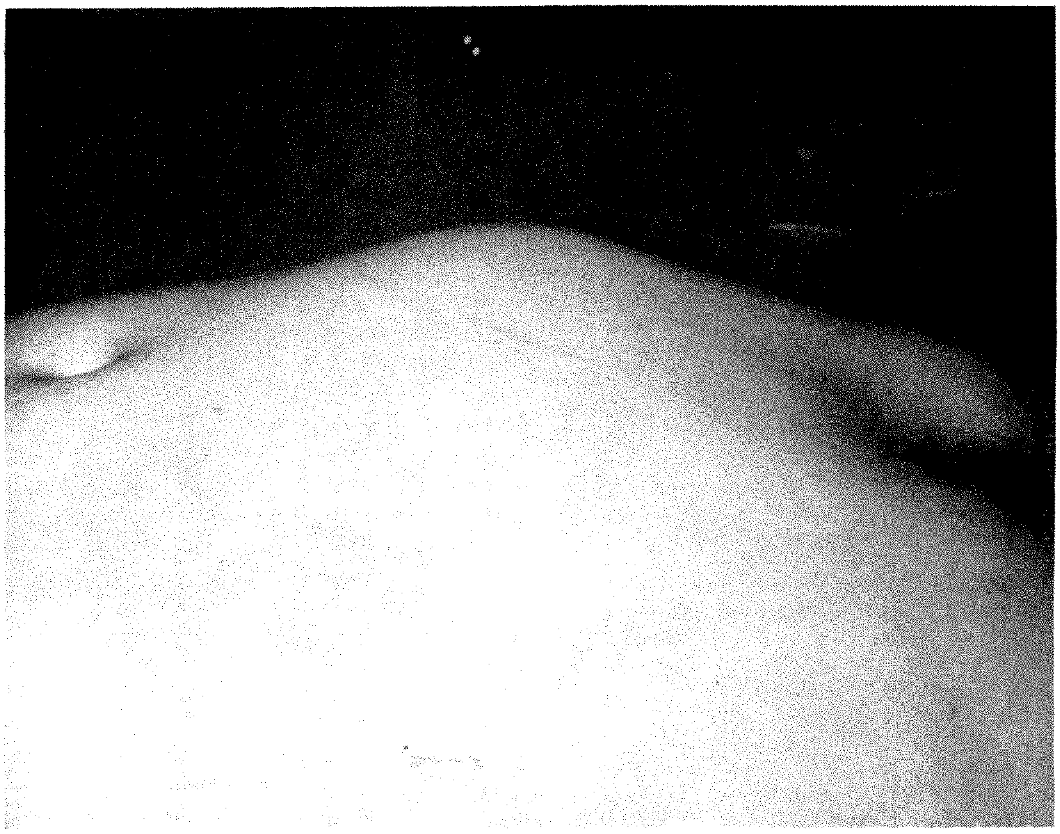

Fig. 3—Right upper quadrant mass that became visible during induction of anesthesia.

## COMMENT

Mentzner[5] reviewed 164 reported cases and presented three additional cases of emphysematous cholecystitis. He found this to be more common in men with a peak age incidence in the sixth and seventh decades. In these patients the incidence of acalculus cholecystitis was nearly three times as frequent as in the nonemphysematous form of the disease. Gangrene was noted in 75% of the cases. Progression to perforation occurred in 20% making this complication five times as frequent with emphysematous cholecystitis as compared to acute cholecystitis. Diabetes mellitus was found to be a predisposing factor. It had no bearing, however, on the development of gangrene, perforation, or over all mortality. The overall mortality of emphysematous cholecystitis was reported as 15% as opposed to 4.1% for acute cholecystitis.

Despite the increased risk of the above mentioned complications, patients with emphysematous cholecystitis exhibited much the same clinical picture as those patients with acute nongaseous cholecystitis. Bigler[6] reviewed 73 cases of emphysematous cholecystitis and reported that pain and tenderness were usually well localized in the right upper quadrant of the abdomen. A mass was palpable on admission in 24 patients and became palpable in an additional seven patients later during the hospital course. Jaundice was present on admission 17 times, yet almost half the initial temperature readings were within the normal range. The remainder of the patients had a temperature between 37 and

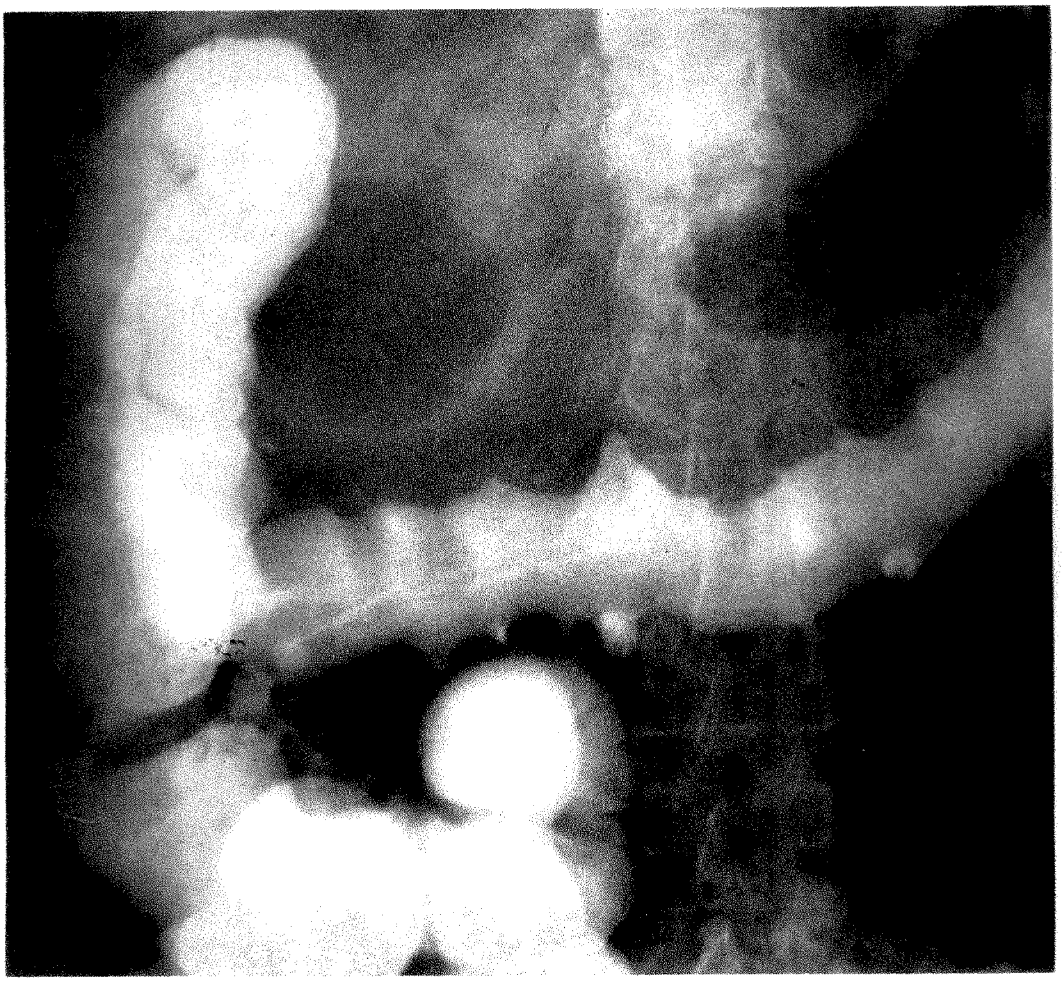

Fig. 4—Barium enema showed the right upper quadrant lucency to be unrelated to the lower gastrointestinal tract.

30° C. Most WBC's were in the range of 12,000-20,000/cu. mm.

Gas-producing organisms invading injured devitalized tissue is one of the major etiologic factors in the pathogenesis of emphysematous cholecystitis.[7] With the proliferation of gas-producing organisms, gas can be identified radiologically in one of the three aforementioned stages. In the second and third stages the diagnosis of emphysematous cholecystitis can be made on the plain film study of the abdomen because the radiographic findings are pathognomonic. It is in the differentiation of the first stage of emphysematous cholecystitis from other entities that confusion results. If gas should be present around gallstones the diagnosis of emphysematous cholecystitis is more easily made. When this marker is absent the following entities should be considered in the differential diagnosis of the radiographic picture of an abnormal gas collection in the right upper quadrant: gas in the duodenum or abnormally positioned bowel, biliary enteric fistula, right upper quadrant abscess, or lipomatosis of the gallbladder. If the clinical picture is not clear, an appropriate contrast study, either an upper gastrointestinal series or a barium enema will aid the localization of the gas in the gallbladder and rule out a suspected associated abnormality of the small intestine. This information taken together with the clinical picture should be sufficient to make the diagnosis of emphysematous cholecystitis.

The authors gratefully acknowledge the helpful criticism of Drs. L. Bernstein and T. Beneventano and would like to thank Drs. M. Zimmelbaum and M. Simon for allowing us to include Case 2.

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# The Last Page

## QUESTIONS IN GASTROENTEROLOGY

CHARLES G. HAZZI, M.D., F.A.C.G.*
New York, N. Y.

*The Last Page* appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the article can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. LOWER ESOPHAGEAL SPHINCTER PRESSURE IN PREGNANCY:

   A. LESP and the LES muscle response to stimulation are both reduced during pregnancy.

   B. Increased plasma progesterone, alone or in combination with estrogen, may explain this reduction in LESP.

   C. Thyrotropin releasing hormone (TRH), normally secreted by the hypothalamus, releases both thyrotropin and prolactin.

   D. TRH intravenously raised serum prolactin to levels found in pregnancy and lowered LESP.

   (Page 259)

2. TUBERCULOUS PERITONITIS AND GALLIUM-67 SCANNING:

   A. Tuberculous peritonitis is always associated with clinical tuberculosis elsewhere.

   B. The dry form is easier to diagnose than the ascitic form.

   C. Gallium-67 may be taken up by both tumor cells and by cells involved in the inflammatory response.

   D. Diffuse intra-abdominal uptake of gallium-67 may lead to an early diagnosis of tuberculous peritonitis.

   (Page 264)

3. ENDOSCOPIC DIAGNOSIS OF GASTRITIS:

   A. Normal appearing mucosa on endoscopy may reveal gastritis on biopsy in up to one-third of cases.

   B. A diagnosis of gastritis on endoscopy is always associated with histologic changes.

   C. Endoscopic diagnosis of atrophic gastritis (reduction in mucosal folds and visible vascular network) is very reliable.

   D. Electron microscopy does not enhance the diagnostic accuracy of light necroscopy.

   (Page 269)

4. TUBULAR STENOSIS OF THE DISTAL COMMON BILE DUCT:

   A. Is due to swelling or fibrosis of the head of the pancreas (extrinsic compression).

---

* Associate Professor of Clinical Medicine, New York University School of Medicine.

B. Occurs with or without gallstone disease.

C. Can only be reliably demonstrated cholangiographically.

D. Never requires choledochoduodenostomy.

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5. SERUM HAPTOGLOBIN IN MALIGNANCIES:

A. Haptoglobin is a gamma-globulin synthesized in the liver.

B. Elevated levels occur in infection, connective tissue diseases and malignancy.

C. The highest levels in malignancies are found with gallbladder and renal carcinomas.

D. High levels are due to production by the tumor.

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6. FOOD IMPACTION OF THE ESOPHAGUS:

A. May be associated with benign or malignant stricture, mucosal ring, motility disorder of inadequate mastication.

B. Has a characteristic appearance on barium swallow.

C. May be rapidly relieved by intravenous glucagon.

D. Glucagon stimulated esophageal peristalsis and has no effect on the sphincter.

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7. LYPHOMA OF THE ESOPHAGOGASTRIC REGION:

A. This is a common presentation of gastrointestinal lymphoma.

B. Radiation is considered the therapy of choice.

C. Stricture of the esophagus may follow high dose radiation (over 6,000 rads) or when lower doses are followed by Adriamycin.

D. Radiation necrosis of the tumor may result in cavitation or perforation.

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8. LYMPHOSARCOMA OF THE SMALL BOWEL:

A. Is the most common malignant tumor of the small bowel.

B. Is more common in the duodenum than in the ileum.

C. May be confused with ulcer or diverticulum on radiologic studies.

D. As with other small bowel neoplasms, is significantly associated with primary malignancies of other organs.

(Page 295)

9. INTRAMURAL HEMATOMA OF THE STOMACH:

A. Is as common as in the small bowel.

B. May be due to trauma or abnormal clotting.

C. May be confused radiologically with neoplasms, gastric varices or extrinsic pressure.

D. May disappear radiologically within a week.

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10. *PNEUMATOSIS CYSTOIDES INTESTINALIS* AFTER JEJUNOILEAL BY-PASS:

A. Involves the by-passed segment of bowel.

B. May be due to a combination of bacterial overgrowth and intermittent obstruction.

C. Is always benign and never causes severe atrophy and fibrosis of the bowel wall.

D. Always responds to inhalation of oxygen or long-tube decompression of the bowel.

(Page 306)

11. *LINITIS PLASTICA:*

A. Is a diffusely infiltrating anaplastic carcinoma that is as common in other hollow organs as in the stomach.

B. Is as commonly primary as secondary to metastatic carcinoma when it involves the colon.

C. When it involves the colon secondarily, is usually metastatic from gastric, gallbladder or breast carcinoma.

D. May be confused with the narrowing and rigidity of inflammatory or ischemic bowel disease when it affects the colon.

(Page 311)

12. POLYPOID LESIONS OF THE COLON:

A. The double contrast barium air enema misses 20% of polyps under 1 cm., while colonoscopy misses 2-5%.

B. After polypectomy, 30% of patients develop recurrence; the rate is higher with villous adenoma or multiple polyps.

C. No case of metastasis has been reported with carcinoma *in situ* which has not penetrated the *muscularis mucosae* of the polyp.

D. Sigmoidoscopic removal of all rectosigmoid adenomas in a group of patients over a period of 25 years decreased the incidence of cancer in that segment by 86%.

(Page 315)

13. EMPHYSEMATOUS CHOLECYSTITIS:

A. Has a greater male incidence and is more commonly acalculous than acute cholecystitis.

B. Does not have a higher rate of complications or mortality than the nonemphysematous form.

C. Is due invasion by gas-producing organisms.

D. Has three radiologic states: collection of gas in the lumen at first, a ring of gas in the wall later and finally, gas in the pericholecystic tissues.

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# BOOK REVIEWS FOR GASTROENTEROLOGISTS

**Surgical Techniques Illustrated, Vol. 3, No. 1, Adrenalectomy, Left Lung Resections: edited by Ronald A. Malt, M.D. 99 pages, illustrated. Little, Brown and Company, Boston, MA, 1978. Price $68.00 per yr.**

This atlas of surgical procedures presents surgical operations, adrenalectomy and left lung resections. Speaking as a surgeon the technics are well illustrated and well annotated. Although meant primarily for the surgical resident and young surgeon, perusal by their medical associates might afford insight into the problems encountered.

David A. Dreiling, M.D., F.A.C.G.

**Medical Examination Review Book, Vol. 22, Gastroenterology, 3rd edition: edited by Lawrence D. Wruble, M.D., Myron Lewis, M.D. and Michael Levinson, M.D. 203 pages, illustrated. Medical Examination Publishing Co., Inc. Flushing, NY, 1977. Price $15.00.**

Surprisingly, this compendium of multiple choice questions designed for "self-evaluation" proves to be entertaining and worthwhile. In today's inflationary period, it is not terribly overpriced. The references, some as recent as 1976, are adequat.e This little book is worthwhile, as the authors state, in "improving one's skills with multiple choice examinations".

Walter Harvey Jacobs, M.D., F.A.C.G.

**Atlas of Gray Scale Ultrasonography: by Kenneth J. W. Taylor, M.D. 411 pages, illustrated Churchill Livingstone, New York, NY, 1978. Price $35.00.**

In these days of scan and sonar, gray scale ultrasonography is becoming one of the most frequently ordered laboratory diagnostic tests. Noninvasive, accurate and relatively inexpensive, it is most useful in disclosing mass and cystic lesions. This atlas, a multi-authored text from Yale Medical School, is extremely well done. Following three introductory chapters elucidating technic, clinical indications and general clinical usefulness, the normal and abnormal anatomy of the liver, biliary tract, pancreas, spleen, kidneys, great vesels, general abdomen and thorax, etc. are presented. The illustrations are plentiful, well reproduced and explained by line drawing. Following my scanning the book, 1grams which looked like gobblydegook to me before, now suddenly make sense.

David A. Dreiling, M.D., F.A.C.G.

**Hepatotrophic Factors: Ciba Foundation Symposium No. 55 (new series). 405 pages, illustrated. Excerpta Medica, Amsterdam, The Netherlands, 1978. Price $36.00.**

*Hepatotrophic Factors* is the report of a Ciba Symposium. It is an absolutely fascinating collection of state of the art papers on liver regenerations and the factors influencing this phenomenon. The role of insulin, glucagon, pancreatic secretion, gastrointestinal hormone, epidermal growth factor, etc. are discussed fully. The final chapters deal with fulminant liver failure, diabetes, glycogen storage disease and hypercholesterolemia. The book should be of interest to the surgeon, gastroenterologist, endocrinologist and biochemist.

David A. Dreiling, M.D., F.A.C.G.

**An Atlas of Scanning Electron Microscopy: The Liver: by Pietro Motta, M.D., Masaki Muto, M.D. and Tsuneo Fujita, M.D. 174 pages, illustrated. Igaku-Shoin Medical Publishers, Inc., New York, NY, 1978. Price $34.50.**

This atlas is a magnificently annotated visual presentation of liver anatomy in health and disease. It is a splendid way to fix in your mind's eye the structure of the hepatic parenchyma, its vascular supply and its conduits. I read through with rapt attention. So will you.

David A. Dreiling, M.D., F.A.C.G.

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# In Memoriam

We record with profound sorrow the passing of: Sigurd W. Johnsen, M.D., F.A.C.G., Life Fellow, Passaic, NJ; David C. H. Sun, M.D., F.A.C.G., Fellow, Phoenix, AZ; Edward Boros, M.D., F.A.C.G., Fellow, Great Neck, NY; Charles S. Lilien, M.D., F.A.C.G., Fellow, N. Miami Beach, FL and William Addleman, M.D., Associate Fellow, Montreal, Que, Canda.

Dr. Johnsen was a Past President of the American College of Gastroenterology and was the first President in 1954 when the National Gastroenterological Association became the present American College of Gastroenterology. Prior to his term of office as President, Dr. Johnsen had been on the National Council and the Board of Trustees of the organization. It was during his term of office also that a new Constitution was adopted which, with minor amendments, still governs the College.

Dr. David C. H. Sun, although a rather recent Fellow of the College, was, at the time of his untimely death, a member of the Board of Trustees and Chairman of the Research Committee. Last year Dr. Sun was Chairman of the Graduate Education Committee and also Chairman of the Course jointly sponsored by the College and the Good Samaritan Hospital in Phoenix, AZ. In 1977 Dr. Sun established the David C. H. Sun Lecture, to be given annually as part of the Postgraduate Course of the College. The first lecturer was J. Edward Berk, M.D., F.A.C.G. of Irvine, CA and last year the lecturer was Rosalyn S. Yalow, Ph.D. of Bronx, NY.

We extend our deepest sympathies to the bereaved families.

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# NEWS NOTES

## GUIDELINES FOR TRAINING IN GASTROINTESTINAL ENDOSCOPY

The revised Guidelines for Training in Gastrointestinal Endoscopy, prepared by the American Society for Gastrointestinal Endoscopy and approved by members of the Federation of Digestive Disease Societies, are now available from the Executive Office of A/S/G/E at the following address: Suite 620, 6 Beacon Street, Boston, MA 02108.

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## PORTUGUESE SOCIETY OF GASTROENTEROLOGY

The newly elected officers of the Portuguese Society of Gastroenterology are: President, Manuel Teixeira Amarante, Jr., M.D., F.A.C.G.; Vice Presidents, Dinis da Silva Freitas, M.D. and Jose Manuel Carriho Ribeiro; General-Secretary, Antonio Cruz Pinho, M.D. and Treasurer, Guilherme Rodrigues Peixe, M.D.

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## COURSE IN HEPATIC, BILIARY AND PANCREATIC SURGERY

The 43rd Annual Course in Hepatic, Biliary and Pancreatic Surgery of the University of Minnesota Dpartment of Surgery-Medical School Continuing Medical Education Program will be given at the West Bank Auditorium of the University of Minnesota in Minneapolis, 13-16 June 1979. Registration and additional information may be obtained by writing to: Registrar, Continuing Medical Education, University of Minnesota, Box 293 Mayo Memorial Bldg., 420 Delaware Street S.E., Minneapolis, MN 55455.

## INTERNATIONAL CONGRESS OF GASTROENTEROLOGY

The XI International Congress of Gastroenterology will take place in Hamburg, Germany, 8-13 June 1980. Further information may be obtained by writing to: Congress Project Management, Günter Sachs, Letzter Hasenpfad 61, D-6000 Frankfurt 70, Germany.

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## AMERICAN PANCREATIC ASSOCIATION MEETING

The annual joint scientific meeting of the American Pancreatic Association and the National Pancreatic Cancer Project will be held on Thursday and Friday, 1 and 2 November 1979, at the Ambassador West Hotel, Chicago, IL. Information concerning the respective meetings should be directed to: Frank P. Brooks, M.D., Executive Secretary, American Pancreatic Association, Inc., Box 652, Hospital of the University of Pennsylvania, Philadelphia, PA 19104 or Isidore Cohn, Jr., M.D., Project Director, National Pancreatic Cancer Project, Louisiana State University Medical Center, 1542 Tulane Avenue, New Orleans, LA 70112.

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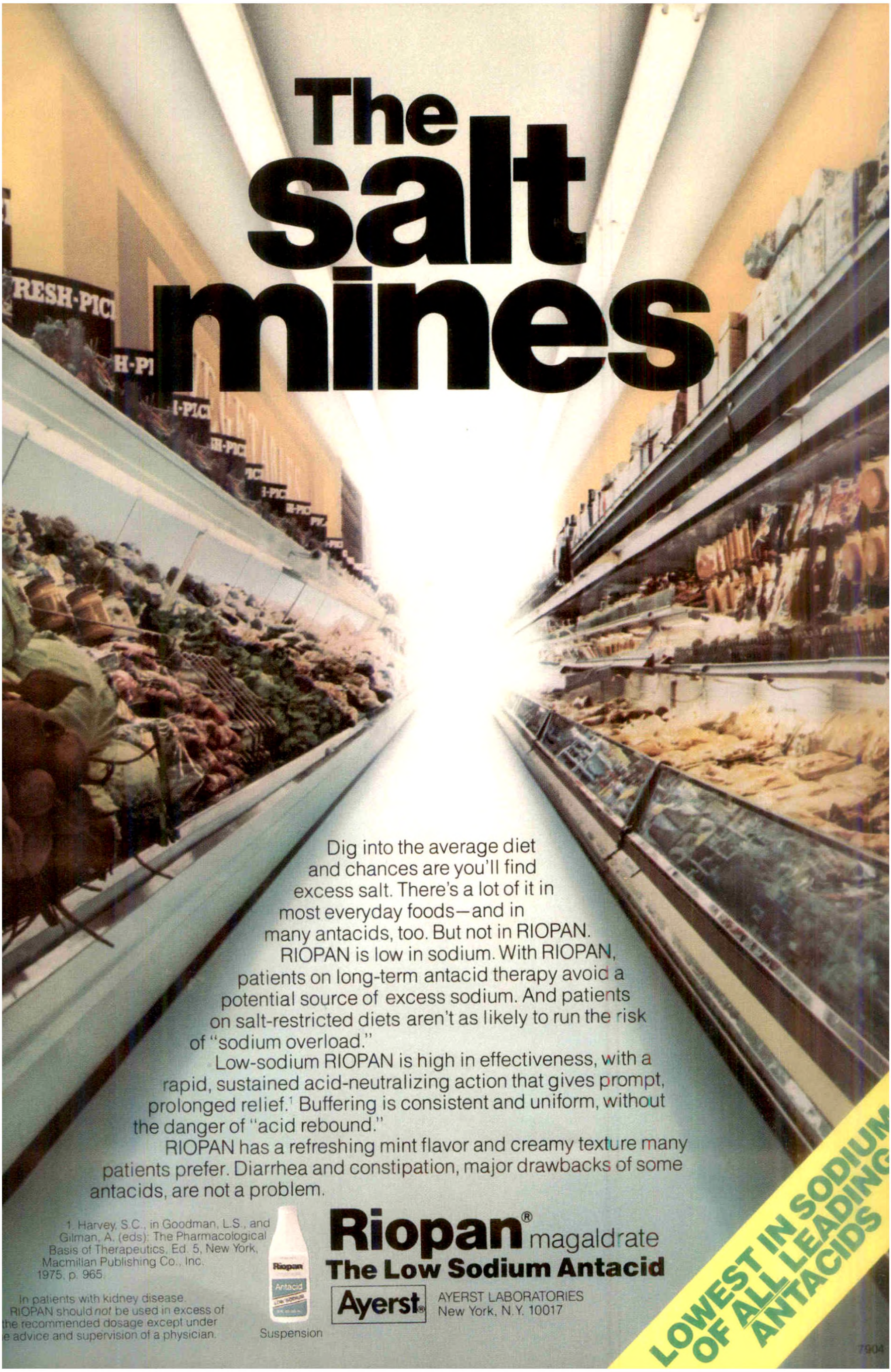
## 2ND INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL EMERGENCIES

The 2nd International Symposium on Gastrointestinal Emergencies will take place in Rome, Italy, 2-8 June 1979 in conjunction with several Italian gastroenterological societies. Further information may be obtained by writing to: CK International srl, Via Giorgia Vasari, 4-00196 Rome, Italy.



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1. Harvey, S.C., in Goodman, L.S., and Gilman, A. (eds): The Pharmacological Basis of Therapeutics, Ed. 5, New York, Macmillan Publishing Co., Inc. 1975, p. 965.

In patients with kidney disease, RIOPAN should *not* be used in excess of the recommended dosage except under e advice and supervision of a physician.

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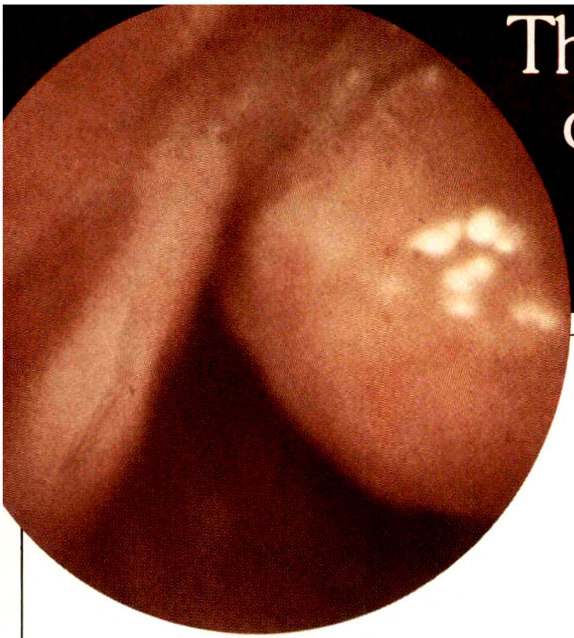
# The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.



# What is the diagnosis?

## Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

*Esophagoscopy* was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

# Endoscopy

### -confirmatory or contradictory-

# a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

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**Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

**Contraindications:** Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.
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As with all anticholinergics, inhibition of lactation may occur.
**Precautions:** In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.
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## MEETINGS OF INTEREST

**44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.**

**Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.**

**Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.**

A Day in the G.I. Tract—An Update for the Generalist and Specialist, Divisions of Gastrointestinal and Liver Diseases, Albert Einstein College of Medicine and Montefiore Hospital and Medical Center, Riklis Auditorium, Albert Einstein College of Medicine, Bronx, NY, 29 April 1979.

Current Concepts in Gastrointestinal Disease, Postgraduate Course of the American Gastroenterological Association, Rivergate Convention Center, New Orleans, LA, 19, 20 May 1979.

Eightieth Annual Meeting of the American Gastroenterological Association, New Orleans Hilton, New Orleans, LA, 21-23 May 1979.

Endoscopy 1979, Postgraduate Course of the American Society for Gastrointestinal Endoscopy, New Orleans, LA, 24, 25 May 1979.

International Symposium on Infant Nutrition and the Development of the Gastrointestinal Tract, State University of New York at Buffalo, Department of Pediatrics and Children's Hospital, Buffalo, Niagara Hilton, Niagara Falls, NY, 3-8 June 1979.

Frontiers of Science and the Liver—A Symposium, In Honor of the 75th Birthday of Hans Popper, M.D., F.A.C.G. (Hon.), Mount Sinai School of Medicine of the City University of New York, 1 Gustave Levy Place, New York, N. Y., 5 June 1979.

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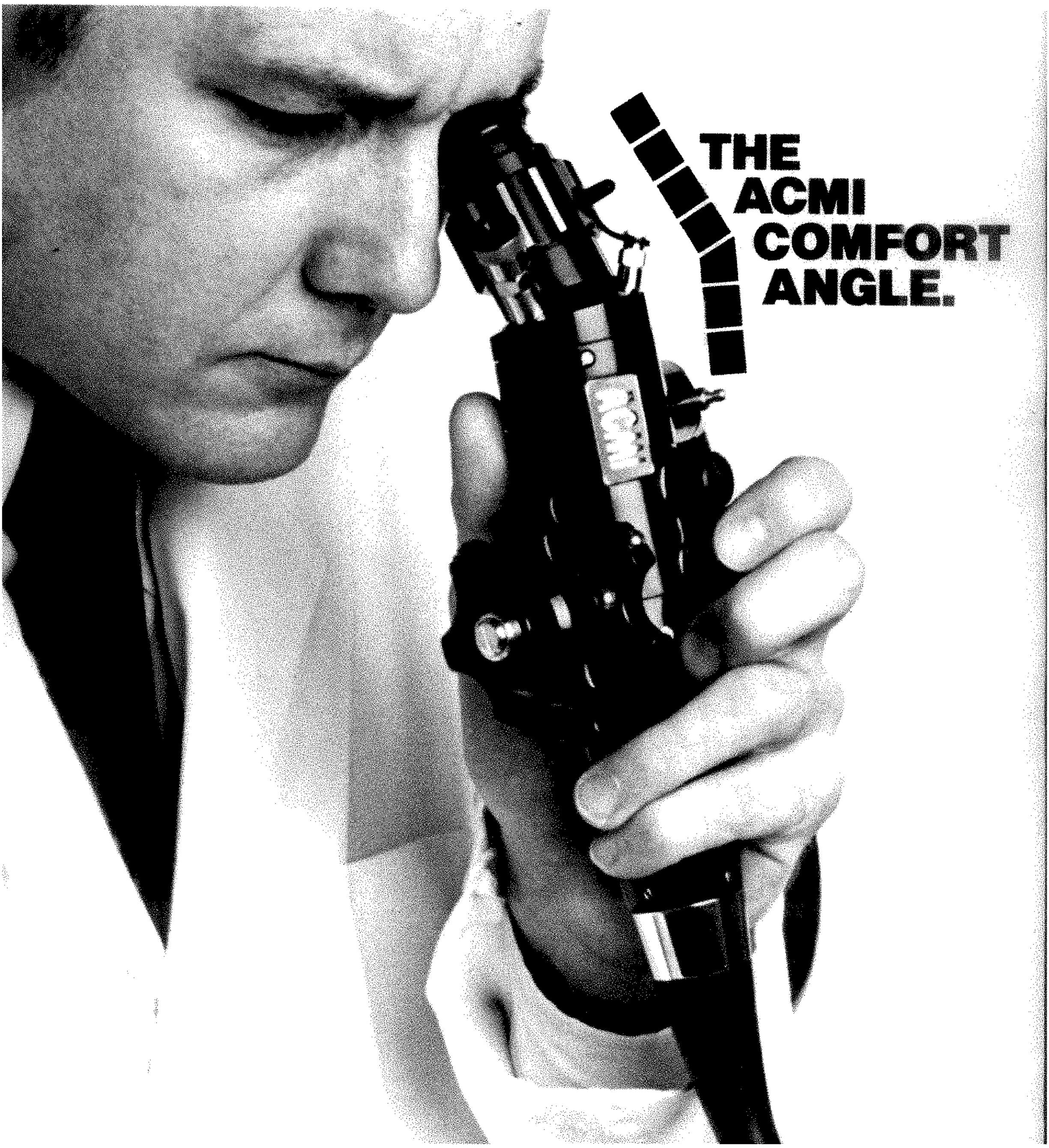

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# 44th Annual Convention of the American College of Gastroenterolog and Course in Postgraduate Gastroenterology

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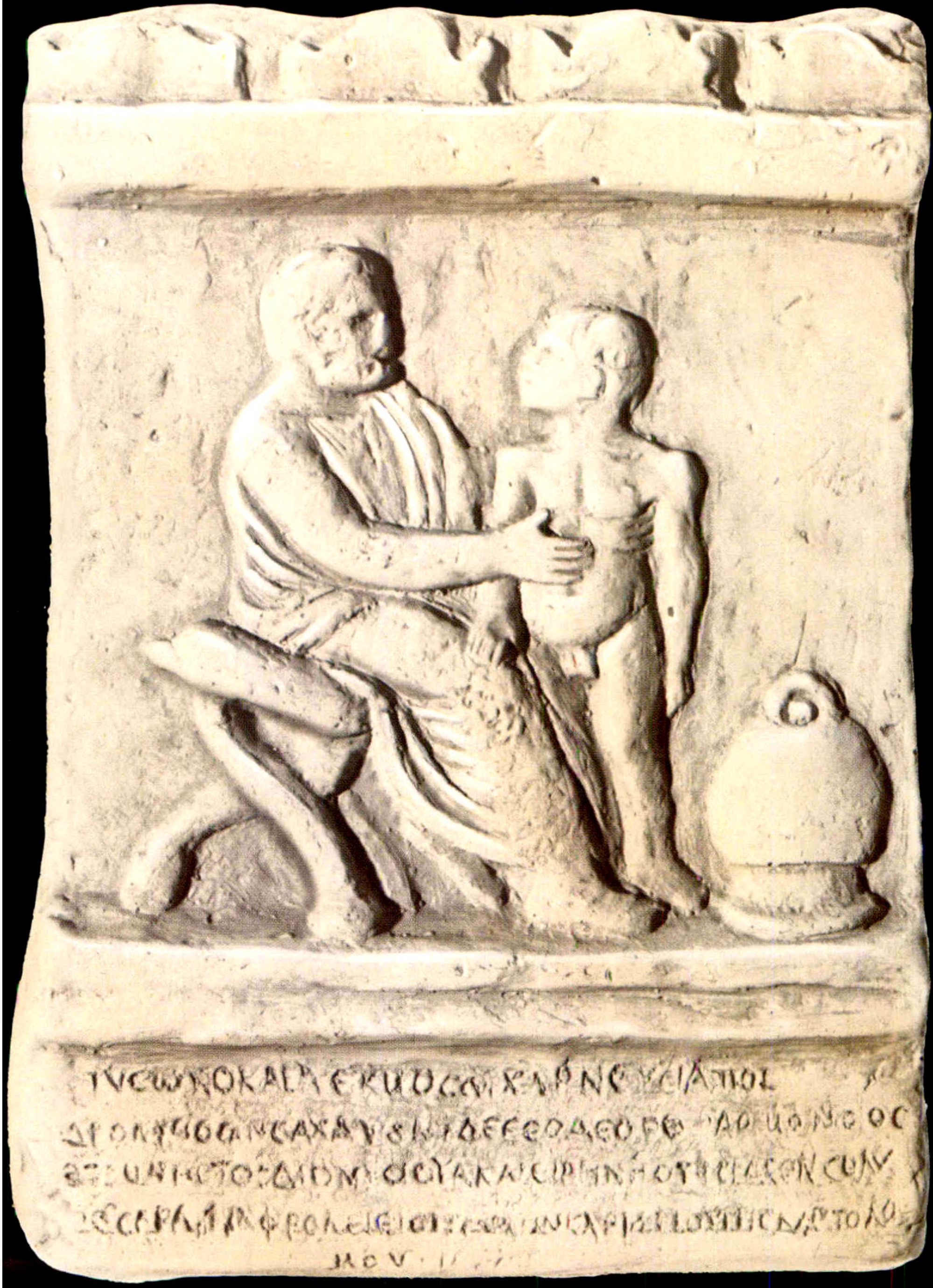

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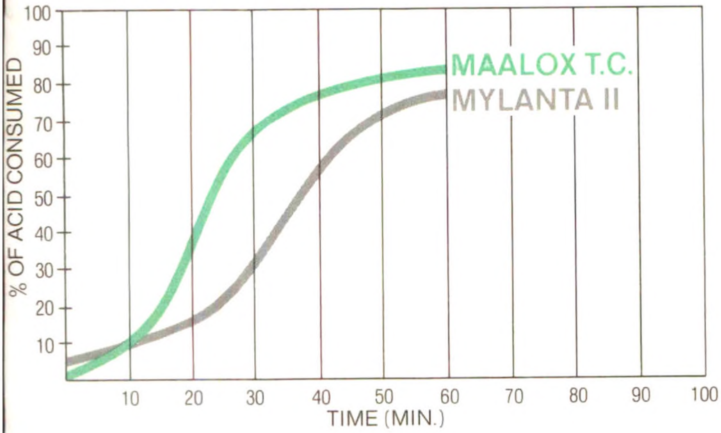

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## A Journal of Clinical Gastroenterology

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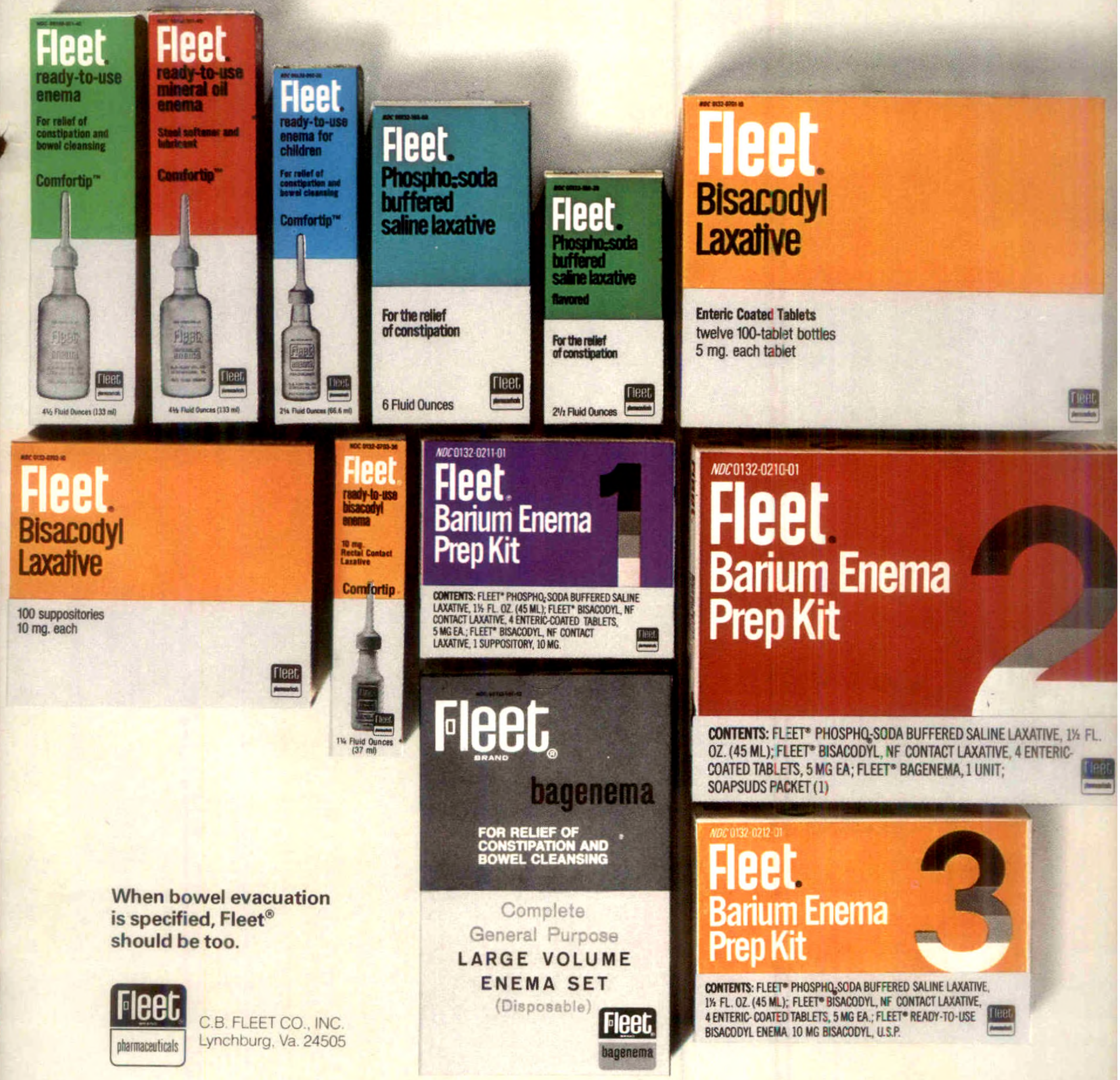
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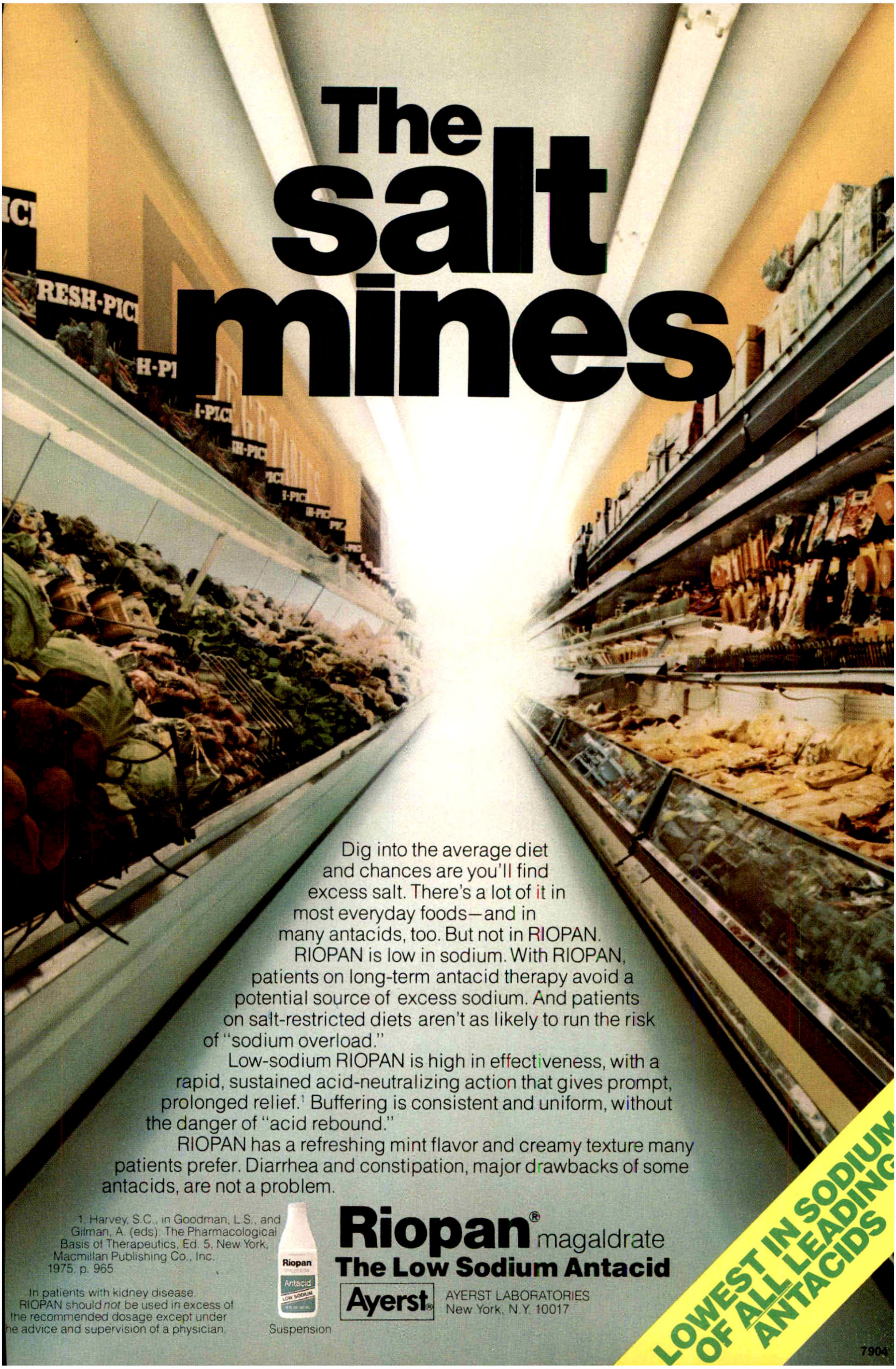

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[1] Harvey, S.C., in Goodman, L.S., and Gilman, A. (eds): The Pharmacological Basis of Therapeutics, Ed. 5, New York, Macmillan Publishing Co., Inc., 1975, p. 965.

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Vol. 71, No. 4 APRIL, 1979

# The American Journal of Gastroenterology

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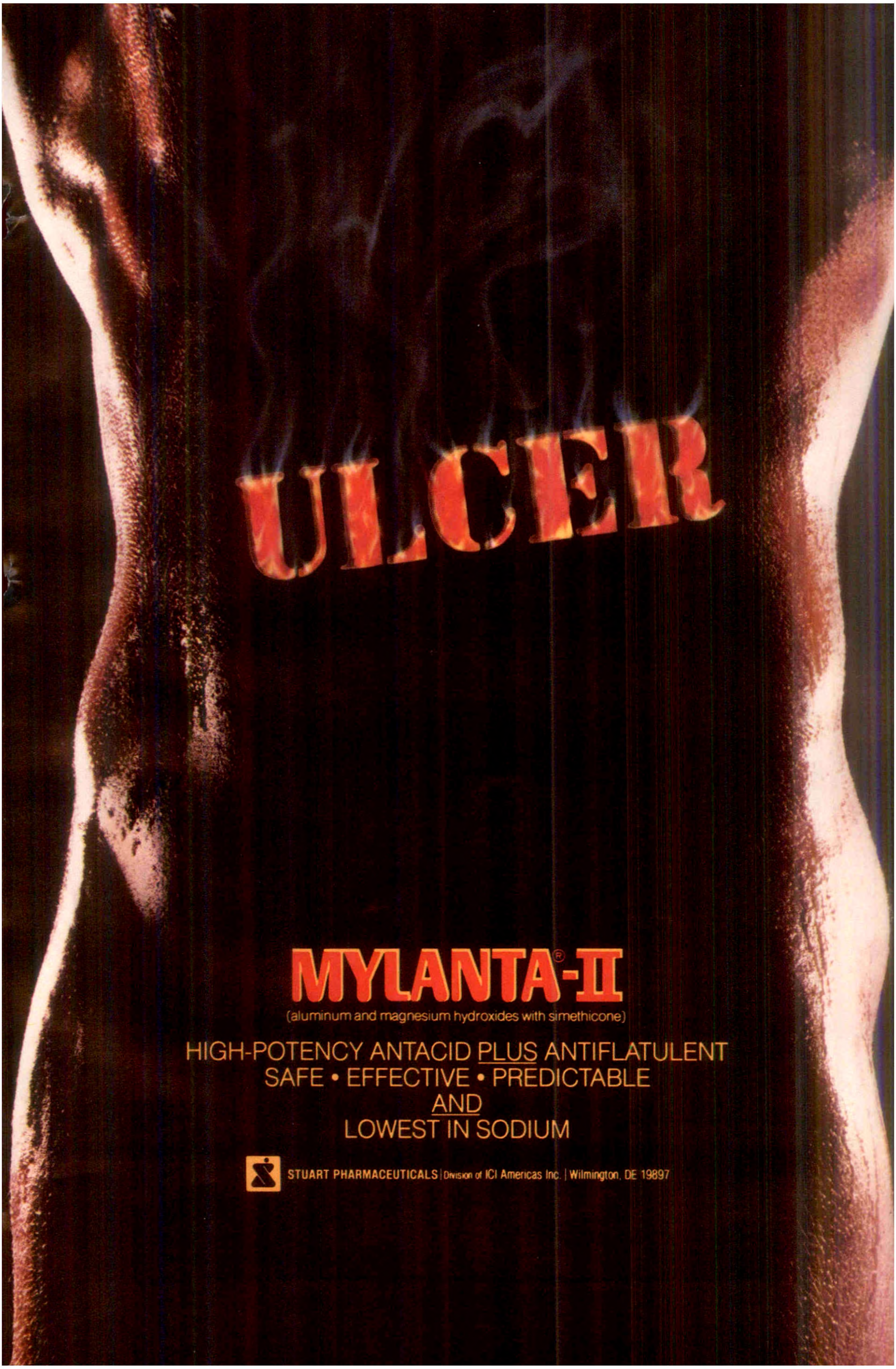

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References to an article with *3 or less authors:*

1. Robinson AS, Sommer DA, Levinson M: Transfiberscopic removal of esophageal polyps. Am J Gastroenterol 61:297-300, 1974.

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Reference to a book:

3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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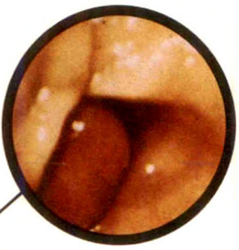

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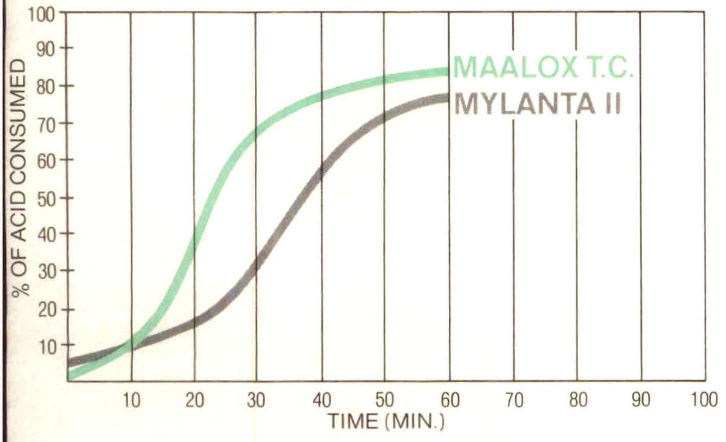

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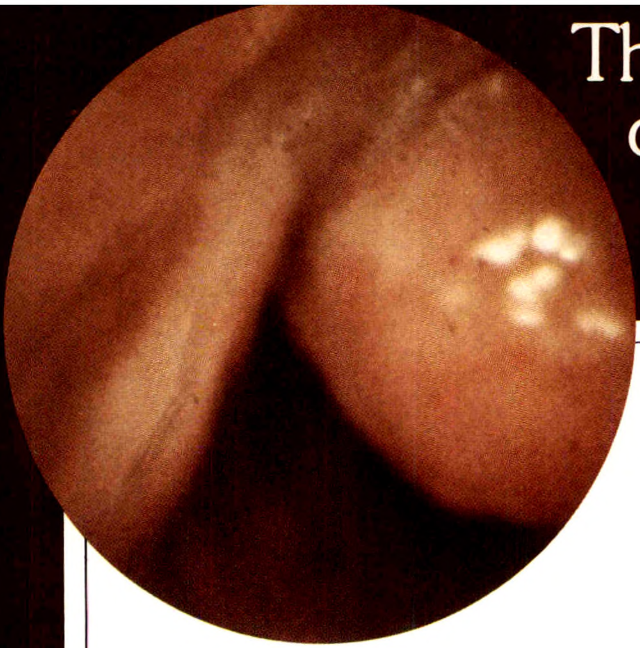

# The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.

# What is the diagnosis?

## Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

*Esophagoscopy* was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

# Endoscopy

## -confirmatory or contradictory-

# a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

# Librax®: a valuable aid in the treatment of irritable bowel syndrome*

The diagnosis of irritable bowel syndrome is based on the patient's symptoms and history, plus the exclusion of an organic disorder. In this condition, Librax has been found doubly valuable as an adjunct to reassurance and counseling because it relieves distressing symptoms of both emotional and somatic origin.

**1 Only Librax provides the specific antianxiety action of Librium®** (chlordiazepoxide HCl), in addition to the antisecretory-antispasmodic actions of Quarzan® (clidinium Br)—both original developments of Roche research.

**2 Librax seldom impairs mental acuity or performance** when given in proper dosage. However, as with all preparations containing CNS-acting agents, patients should be cautioned against hazardous occupations requiring complete mental alertness.

**3 Flexibility of dosage helps meet varying requirements:** 1 or 2 capsules three or four times daily, before meals and at bedtime.

**4 The convenience and economy of a single Rx** help sustain patient compliance, while providing relief of both emotional and somatic symptoms.

## A distinctive antianxiety-antispasmodic agent

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Each capsule contains 5 mg chlordiazepoxide HCl
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Please see brief summary of prescribing information on following page.

# Librax®

**Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.**

**Please consult complete prescribing information, a summary of which follows:**

**Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

**Contraindications:** Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

**Precautions:** In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

**Adverse Reactions:** No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

**Dosage:** Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

**How Supplied:** Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

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## MEETINGS OF INTEREST

**44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.**

**Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.**

**Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.**

Current Concepts in Gastrointestinal Disease, Postgraduate Course of the American Gastroenterological Association, Rivergate Convention Center, New Orleans, LA, 19, 20 May 1979.

Eightieth Annual Meeting of the American Gastroenterological Association, New Orleans Hilton, New Orleans, LA, 21-23 May 1979.

Endoscopy 1979, Postgraduate Course of the American Society for Gastrointestinal Endoscopy, New Orleans, LA, 24, 25 May 1979.

International Symposium on Infant Nutrition and the Development of the Gastrointestinal Tract, State University of New York at Buffalo, Department of Pediatrics and Children's Hospital, Buffalo, Niagara Hilton, Niagara Falls, NY, 3-8 June 1979.

Frontiers of Science and the Liver—A Symposium, In Honor of the 75th Birthday of Hans Popper, M.D., F.A.C.G. (Hon.), Mount Sinai School of Medicine of the City University of New York, 1 Gustave Levy Place, New York, N. Y., 5 June 1979.

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# Which type of duodenal ulcer patient benefits most from 'Tagamet'?

- ☐ newly diagnosed patients
- ☐ duodenal ulcer repeaters
- ☐ refractory patients
- ☐ hospitalized patients
- ☑ all of the above

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# In all types of duodenal ulcer patients

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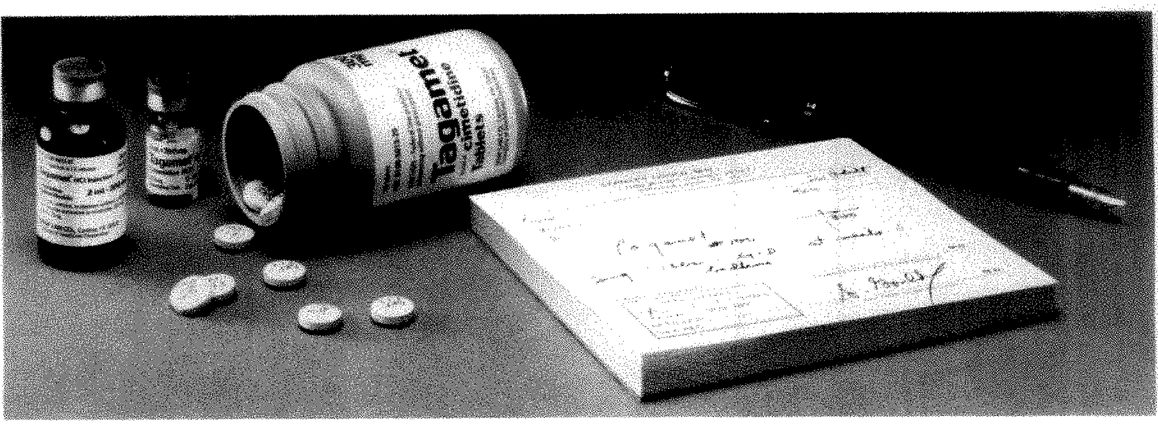

**Dosage in Duodenal Ulcer**

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

**Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.**

**Indications:** 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer, and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

**Contraindications:** There are no known contraindications to the use of 'Tagamet'.

**Precautions:** In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Potentiation of warfarin-type anticoagulants has been observed with concomitant 'Tagamet' administration. For this reason, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when these drugs are administered concomitantly.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

**Adverse Reactions:** Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

**How Supplied: Pale Green Tablets:** 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

**Injection:** 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials, in packages of 10.

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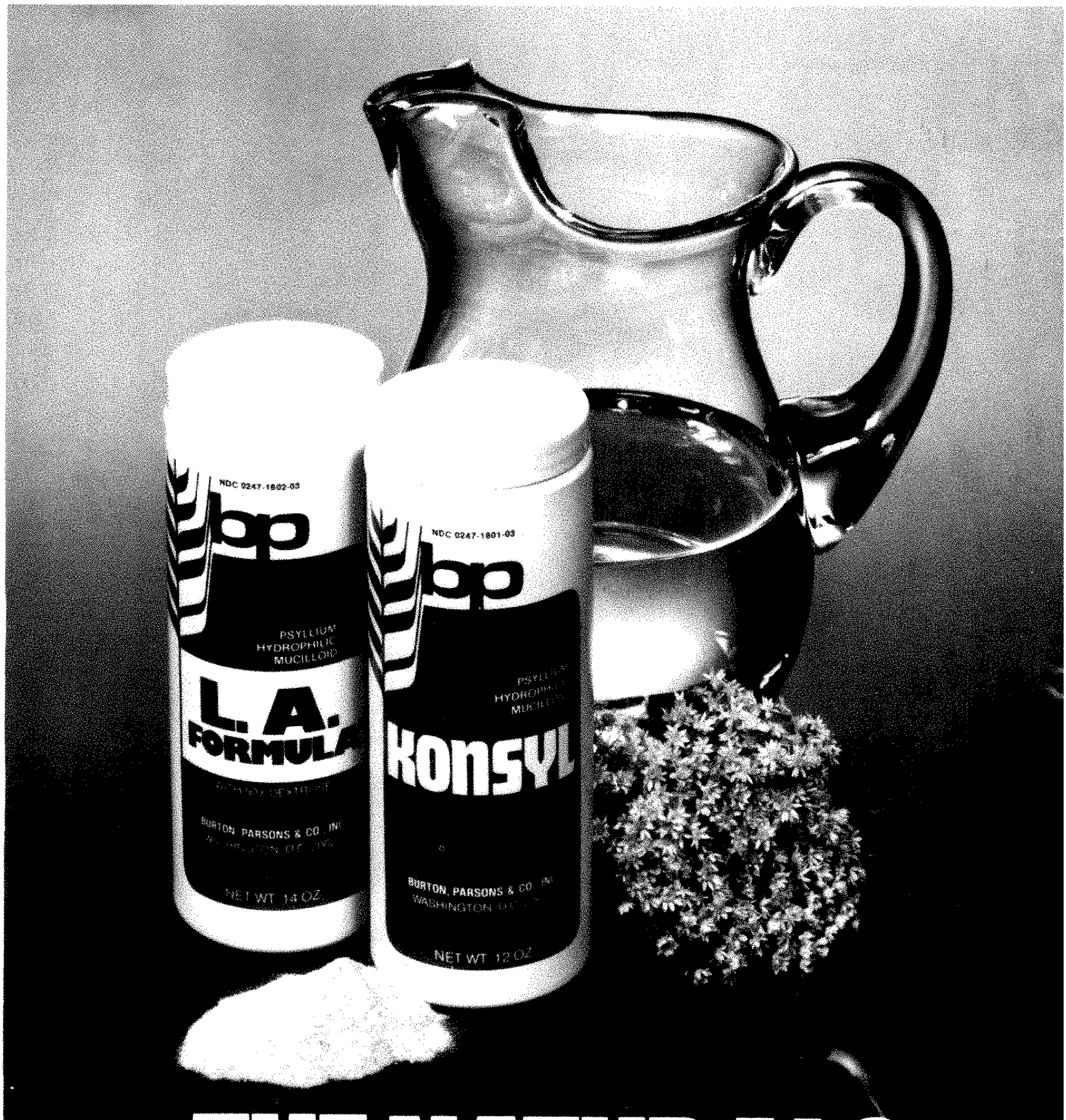
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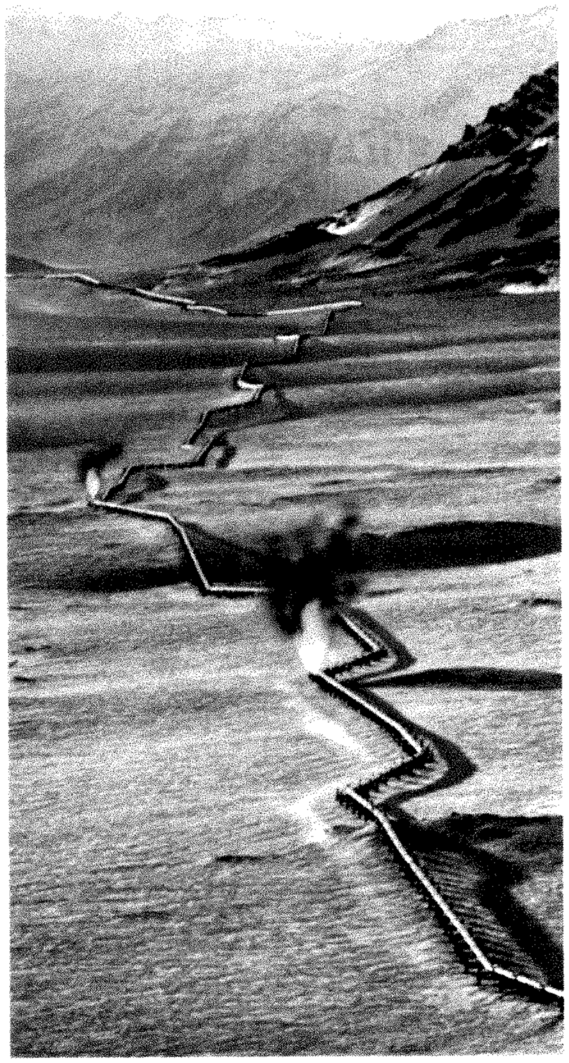
# Avoid U.C. flare-up over the long haul.

Ulcerative colitis is a chronic disease. The best way to prevent relapse: Long-term medication with Azulfidine® (sulfasalazine, N.F.).[1-6] A double-blind study[1] comparing Azulfidine against a control group receiving placebo resulted in a 4½ times greater relapse rate for non-Azulfidine-treated patients.



Simulated flares on a pipeline intended to represent acute exacerbation of chronic ulcerative colitis. Copyright © 1978, Pharmacia Inc

## AZULFIDINE® Tablets and EN-tabs®

(sulfasalazine, N.F.)

**INDICATIONS:** AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.

**CONTRAINDICATIONS:** Hypersensitivity to sulfonamides or salicylates; in infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.

**WARNINGS:** The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.

Complete blood counts as well as urinalysis with microscopic examination should be done frequently.

**PRECAUTIONS:** Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.

Maintain adequate fluid intake to prevent crystalluria and stone formation.

**ADVERSE REACTIONS:** Adverse reactions have been observed in 5 to 55 % of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.

**Blood dyscrasias:** Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, Heinz Body anemia, purpura, hypoprothrombinemia, cyanosis, and methemoglobinemia.

**Hypersensitivity reactions:** Generalized skin eruptions, erythema multiforme (Stevens-Johnson syndrome), parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, pruritus, urticaria, photosensitization, anaphylaxis, serum sickness syndrome, chills, drug fever, periorbital edema, conjunctival and scleral injection, arthralgia, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, L.E. phenomenon, and hepatitis with immune complexes.

**Gastrointestinal reactions:** Anorexia, nausea, emesis, abdominal pains, diarrhea, bloody diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

**CNS reactions:** Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.

**Renal reactions:** Crystalluria, hematuria, proteinuria, and nephrotic syndrome. Toxic nephrosis with oliguria and anuria.

Incidents of alopecia and reduction in sperm count and viability have also been reported.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross sensitivity may exist with these agents.

AZULFIDINE (sulfasalazine, N.F.) produces an orange-yellow color when the urine is alkaline. Similar discoloration of the skin has also been reported.

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**IMPORTANT:** See full prescribing information before administering AZULFIDINE.

**References:**

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Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

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**PRECAUTIONS:** Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
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*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
**DOSAGE AND ADMINISTRATION:** CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
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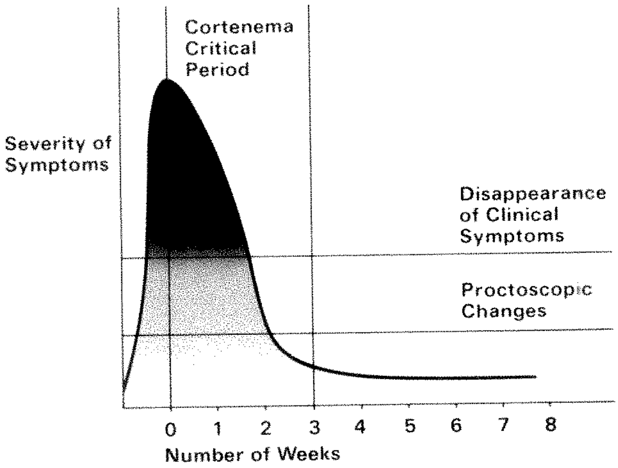

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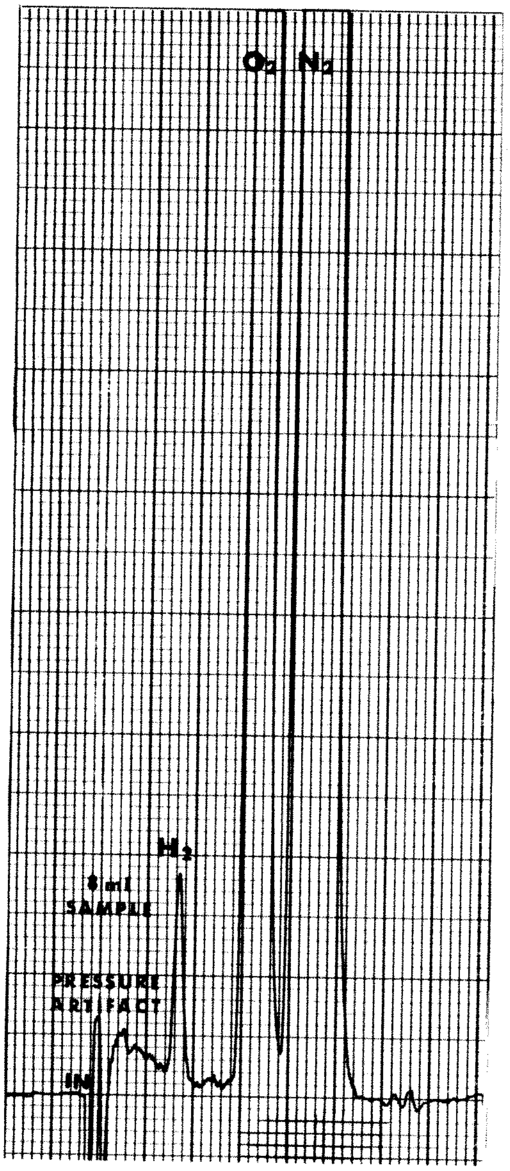

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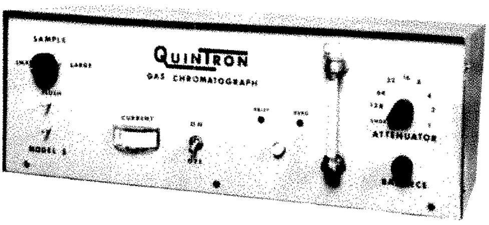

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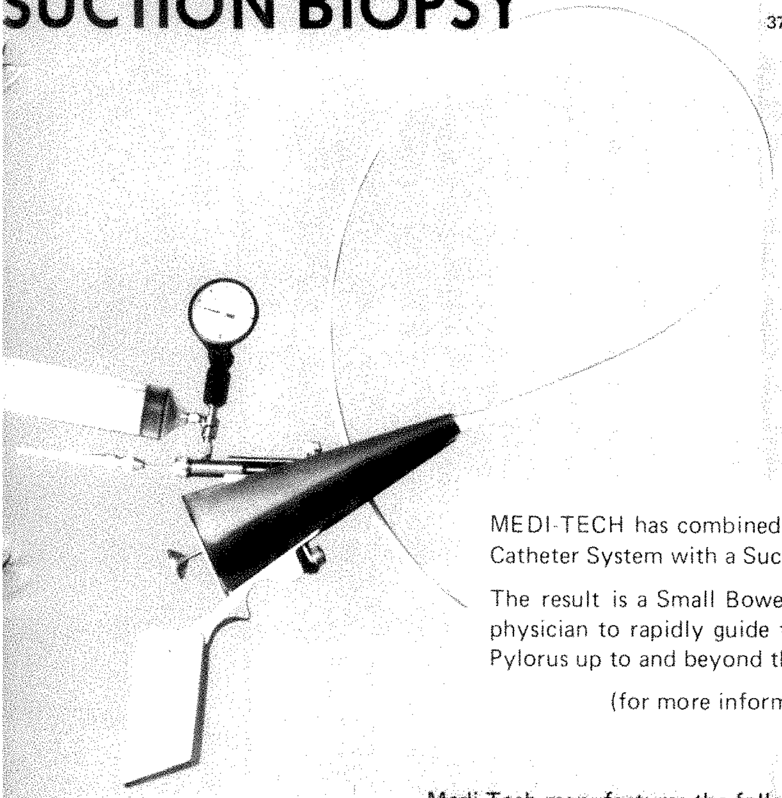

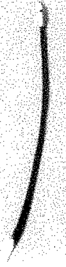

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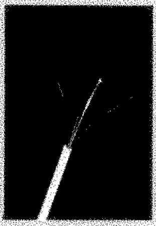

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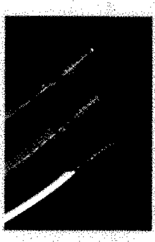

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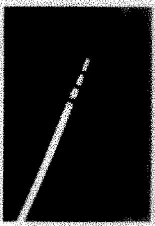

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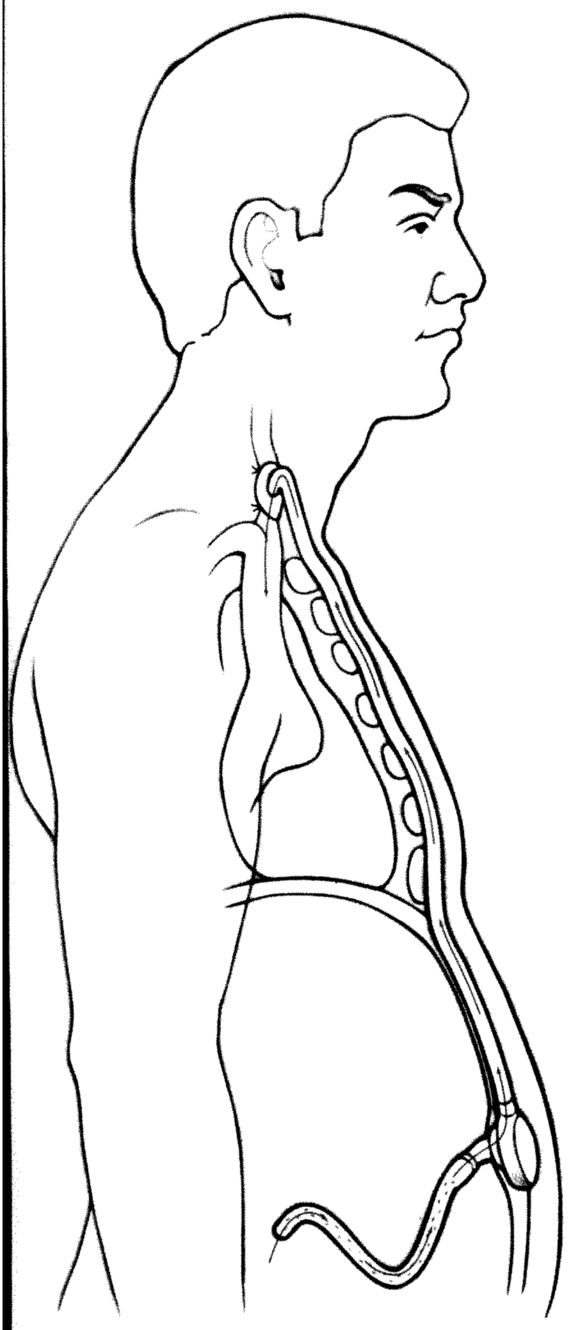
# In refractory ascites the LeVEEN Peritoneo-Venous Shunt can achieve dramatic results



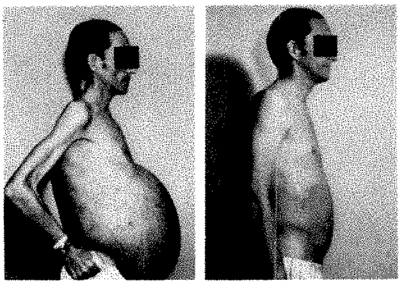
The LeVEEN Peritoneo-Venous Shunt can improve the prognosis of patients with ascites who become refractory to medical measures. It offers significant improvement in the control of ascites and reduces morbidity of such patients. The shunt can be used in ascites of varying origin.

## Removes and prevents fluid buildup

Implanted permanently in a simple surgical procedure, the LeVEEN Peritoneo-Venous Shunt returns peritoneal fluid to the superior vena cava through a pressure-sensitive extraperitoneal valve. Through continuous reinfusion of the patient's own ascitic fluid, the shunt removes and prevents fluid buildup.

## Clinical experience

Postoperative improvement following insertion of the LeVEEN Peritoneo-Venous Shunt is often dramatic, particularly in the reduction of abdominal girth. Improvement is generally evidenced by: reduced weight, increased urine output, improved renal function, lowered BUN and creatinine levels, reduced aldosterone, elevated plasma protein (with a return of the albumin-globulin ratio toward normal), and greater patient comfort, mobility and ease of breathing. In many patients with marked wasting before surgery, appetite is improved and body mass is regained postoperatively.[1]



*Typical girth reduction in patient after shunt installation.*

**Dramatic relief of symptoms.** To date, the LeVEEN Peritoneo-Venous Shunt has been placed in more than 1,100 patients throughout the world. In one reported series of patients whose serum bilirubin was less than 10mg/100 ml, who had no evidence of severe encephalopathy, and no recent episode of upper gastrointestinal bleeding, 71% were alive 18 months later. At 18 months, these survivors had exceeded the survival rate expected for patients with refractory ascites treated with other accepted methods.[2]

For further information about the LeVEEN Peritoneo-Venous Shunt and its clinical experience, write to Ms. Peggy Harding, Becton, Dickinson and Company, Rutherford, N.J., 07070, or call this toll free number for answers to your technical questions: 800-631-0174. In New Jersey call 201-460-2251.

**The LeVEEN Peritoneo-Venous Shunt.**

**The reinfusion shunt controls ascites through continuous reinfusion of the patient's own ascitic fluid.**

*The LeVEEN Peritoneo-Venous Shunt is an in vivo device containing a unique, one-way valve which permits the unidirectional flow of ascitic fluid from the abdomen to the vascular system whenever the intraperitoneal pressure exceeds the central venous pressure by 3 cm. of water.*

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**Indications For Use:**
The LEVEEN Peritoneo-Venous Shunt may be indicated when the patient does not respond promptly to intensive medical management.

The shunt is designed to eliminate the accumulation of ascitic fluid. Shunt placement should be considered for treatment of ascites complicating the following conditions:

1. Cirrhosis
2. Budd-Chiari Syndrome
3. Chylous Ascites
4. Nephrogenic Ascites
5. Biliary Atresia
6. Amyloidosis
7. Cryptogenic Ascites

**Contraindications For Use:**
In certain patients, the LEVEEN Peritoneo-Venous Shunt will not be effective, or may be contraindicated because of secondary complications that outweigh its benefits. These conditions are:

1. **Peritonitis.** This should always be suspected when the peritoneal fluid is turbid. Peritonitis can occur without the usual signs and symptoms in patients with ascites.
2. **Esophageal Varices with a Recent History of Bleeding.** If ascites and variceal bleeding are present concurrently, treating the varices first may be indicated.
3. **Renal Failure.** The shunt will not reverse the renal damage in patients with acute tubular necrosis or other types of primary renal failure. A low urine sodium concentration may be the best indication that the tubules are functional and may respond to a shunt.
4. **Bilirubin level above 10 mg/dl.**

**Cautions:**

1. **Esophageal Varices without Recent Bleeding.** In patients whose varices have been treated surgically, the shunt may be effective.
2. **Neoplastic Ascites.** The LEVEEN Peritoneo-Venous Shunt has been used with success in patients with intractable ascites associated with primary or metastatic intra-abdominal neoplasms.[2] The use of the shunt in such patients requires weighing the shunt's potential benefits against the possible hazard of generalized dissemination of neoplastic cells which are commonly present in the ascitic fluid of these patients.
3. **Associated Cardiac Disease.** Cardiac patients may be sensitive to increased blood volume due to sudden recirculation of large quantities of ascitic fluid. Removal of accumulated ascitic fluid from the abdomen at the time of shunt placement may be indicated in such patients.

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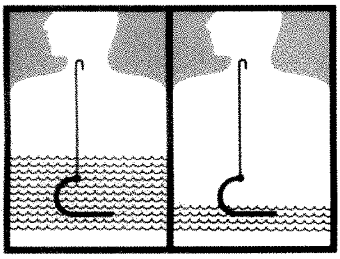

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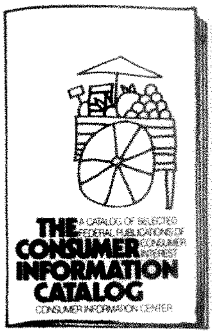
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in irritable colon*

# When stress makes waves for the spasm reactor...

A normal reaction to emotional stress is a marked increase in both the strength and frequency of wave-like contractions of colonic motility.[1] However, in the patient with irritable bowel syndrome, this psychovisceral reaction is of greater intensity and duration than normal.[2]

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**References: 1.** Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy), or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.

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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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VOLUME 71 APRIL, 1979 NUMBER 4

# PRESIDENTIAL ADDRESS*

## THE DOCTOR-PATIENT RELATIONSHIP: ITS PRESENT STATE

WILLIAM S. ROSENTHAL, M.D., F.A.C.G.
Valhalla, NY

During the past 20 years, a number of forces have increased to make the patient more and more estranged from the physician.

There are several factors which play a role in this. One of the leading items is the unprecedented development of technology for the diagnosis and treatment of disease. The ability to study critically almost any area of the gastrointestinal tract or its associated organs has pre-empted those long, largely unresolved, bedside discussions with the house staff and assorted consultants. The only real resolution of roentgenological atypical gastric ulcer used to be surgical exploration. How many patients waited three to six weeks or longer for a decision to operate? How many cancers spread during this period? How many unnecessary operations were performed? What a tremendous difference it is to look at the films, discuss the roentgen criteria for benign vs. malignant ulcer and schedule the patient for endoscopy, biopsy and cytology in the morning.

This change in approach has been extremely satisfying for the physicians, removing much of the uncertainty concerning serious diagnosis. There are obvious benefits for the patient.

There are however, some unforunate side-effects. For example, the gastroenterologist has become more and more preoccupied with procedures. They begin to occupy a significant portion of the work day. Scheduling and equipment maintenance become major activities. As a result, a proportionally smaller part of the day is available for the traditional doctor-patient interaction. Whatever impressive findings are brought to light in the clinical laboratory, the radiology department, or in the endoscopy room, the patient is only aware of what is brought out during his discussion with the doctor. Even the most well-intentioned and unhurried doctor needs a special genius to translate modern technology into understandable English. But a hurried, harried clinician rushing to his next emergency, or even worse, to his next committee meeting is not in a position to communicate well. Often his communication is supplemented by input from house staff, medical students, or paramedical personnel—leading to an extremely garbled version of the facts. This often leads to a patient who has received the best care in technological terms but hasn't a clue about precisely what he has received. All he knows is that a bill has been generated, which may or may not be covered by his insurance.

---

* Delivered at the 43rd Annual Convention of the American College of Gastroenterology, Denver, CO, 25, 26, 27 October 1978.

Another problem posed by our array of potent diagnostic weapons is the patient with an elusive diagnosis. Twenty years ago, even the most curious doctor had to admit that symptoms were functional in origin after what would presently be considered a minimal work-up. Today, we have all sorts of wonderful and expensive tests to augment our history and physicals. Now, when the physician finally admits to himself that the symptoms were really functional, the patient may be presented with an enormous bill and feels no better—perhaps worse. One possible benefit the patient derives is that he has a great story to tell his friends. A story, which repeated over the years by many, has slowly but steadily built up a climate of public dissatisfaction.

This dissatisfaction has also grown out of misuse of the news media and has not been only the result of distortion of facts by sensation-seeking journalists. At least equally important has been the stream of news releases by physicians and laboratory scientists. Almost every night there is a major scientific breakthrough on television. You can pick up a magazine at random and find out that by following ten simple rules, you can play-winning tennis into your seventies or later. These articles are often written by "eminent scientists". From this, public expectation is at a high level. A recent series of hearings produced the conclusion that we were not winning the war over cancer!

Our countrymen cannot understand why, when they become ill, there may be difficulties in diagnosing or tr problem. A treatment failure the be the fault of the doctor; th resentment and litigation.

This climate of public di has led to pressure for lega Laws are passed to ensure physi tence, even though adequate competence does not exist. Ther data that the measures taken to petence have any impact on th which the individual physici practices medicine. Audit proce creasing stringency are being used. We are currently conte variety of laws which are change the entire health care tem without adequate hard d cate that any of the existing mo the world are better or even as one we have.

Existing legislation has alre in major changes in funding n by governmental sources. It i law that he who holds the pur deferred too. Often in the do relationship, the purse string one or another outside agency of this power of the purse stri the deference due the patient Part of the time which might spent providing a better explan disease process and measures t it is now spent filling out va Meticulous care must be taken forms. If not, instead of paym ceives a new set of forms.

What is to be done? I belie allow things to proceed in path, the practice of medicine increasingly more difficult an factory to both doctor and pat

First and foremost, we m ourselves. Are we communicati

Does the patient know why procedures are being done? Why treatment is being delayed? Has the prognosis been properly discussed? Is the family aware of the situation? These questions and more cannot be dealt with by a cheery good morning and wave from the doorway. Improvement of the relationship between doctors and patients can only be accomplished by adequate patient understanding—no matter how good the back-up science.

In addition to this fundamental self-reevaluation, a strong public relations effort must be undertaken. Although community service by individual physicians is a traditional method to accomplish this, another aspect of this can be carried out by major national organizations. The American Medical Association comes to mind as such an organization. While each of their approaches has caused different responses in individual physicians, I believe the sum of their activities is positive. The AMA is not a monolithic organization. Steps can be taken to influence AMA actions at local, regional and national levels.

Above all, this is not a time to retreat into one's shell and declare a pox on all their houses. One must be an activist in the improvement of the doctor-patient relation, both individually in one's office and collectively in society at large.

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# Significance of Endoscopically Visible Blood Vessels as an Index of Atrophic Gastritis*

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The endoscopic criteria for atrophic gastritis are. 1. pale mucosa; 2. shiny surface and 3. prominent submucosal vessels. To evaluate the diagnostic accuracy of circumscribed atrophic gastritis based on these findings, we studied 184 consecutive upper gastrointestinal endoscopies. The endoscopic diagnosis of atrophic gastritis was made only if two endoscopists both agreed on the findings and interpretation. The location of the atrophic pattern and whether it was circumscribed or diffuse were recorded. Two biopsy specimens were then obtained. Histologic material was interpreted by a pathologist who had no prior knowledge of the endoscopic findings. Twenty-five patients (13%) had atrophic gastritis endoscopically; in four it was diffuse and in 21 it was circumscribed. Utilizing the criteria of Whitehead, et al, atrophic gastritis was diagnosed histologically in three of four patients with diffuse gastritis but in one of those considered to have circumscribed atrophic gastritis. It is concluded from these preliminary data that a circumscribed atrophic mucosal pattern is a frequent endoscopic finding that does not necessarily represent atrophic gastritis histologically.

Atrophic gastritis is a diffuse lesion of the gastric mucosa which particularly involves the body and fundus of the stomach.[1-3] Reduction or absence of the glandular layer in the gastric mucosa[4] remains the histologic landmark of this condition. On the basis of their experience with flexible (semi-rigid) gastroscopy, Schindler[5] in 1947 and Palmer[6] in 1949 established increased translucency of the mucosa and visible submucosal blood vessels as criteria for the endoscopic diagnosis of atrophic gastritis. Even with the subsequent advent of fiberoptic endoscopy, these features continue to be regarded as the criteria for the endoscopic diagnosis of atrophic gastritis. Largely neglected are the improved mucosal illumination and light transmission and the narrower visual fields with the fiberoptic endoscopes as compared with the original flexible gastroscope.[7] These act not only to allow greater detail to be made out but also reduce the amount of mucosa seen. As a consequence, submucosal blood vessels are noted much more often than with the older instruments.

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TABLE I

ENDOSCOPIC AND HISTOLOGIC CORRELATION

| Endoscopic finding | No. pts. | Histologic diagnosis | | | % correlation |
|---|---|---|---|---|---|
| | | N* | S G† | A G‡ | |
| 1. Visible submucosal blood vessels | | | | | |
| Diffuse | 4 | 0 | 1 | 3 | 75 |
| Circumscribed | 21 | 13 | 7 | 1 | 4 |
| 2. Normal mucosa | 26 | 23 | 1 | 2 | 88 |

* Normal
† Superficial gastritis
‡ Atrophic gastritis

The intent of this study was to evaluate: 1. the frequency of endoscopically visible blood vessels in the gastric mucosa; 2. the geographic distribution of this endoscopic sign and 3. the reliability of this finding as an index of atrophic gastritis.

## MATERIALS AND METHODS

One hundred eighty-four consecutive patients, undergoing upper gastrointestinal endoscopy for a variety of symptoms, were evaluated. The study group consisted of 98 males and 86 females, ranging in age from 21-67 years, with a mean of 43 years.

Endoscopic preparation included a topical 14% Benzocaine oropharyngeal spray and a mixture of meperidine and diazepam given intravenously. The ACMI-F8 panendoscope was utilized and particular attention paid not to inflate the stomach[8] through the study. Endoscopic diagnosis of prominent, visible submucosal blood vessels, their locations and whether they were diffuse or circumscribed were made only if two endoscopists independently agreed on the findings. Twenty-six patients who had essentially negative endoscopic examination served as controls. Two pinch mucosal biopsy specimens were obtained under direct visualization from the area of abnormality in patients and from normal mucosa of the body and antrum in control subjects. Tissue specimens were placed on a small piece of filter paper and immediately immersed in formalin solution. Standard hematoxylin and eosin stains were employed routinely and special stains were used when indicated.

Histologic material was reviewed and interpreted by a pathologist who had no prior knowledge of the endoscopic findings. In the diagnosis of chronic gastritis, the type of mucosa under study, the grade of gastritis, the activity of the inflammatory process and the presence and type of metaplasia were taken into account, as adopted by Whitehead and his colleagues.[4]

A gastric secretory study was performed on a separate day. Gastric intubation was done under fluoroscopic guidance and pentagastrin (6 mcg./kg.) was used for stimulation.

## RESULTS

Visible submucosal blood vessels were noted in 25 or 13% of the patients. This finding was diffuse in four, involving the body and antrum and was circumscribed in 21. In 16 they were located in the antral region and in five in the body.

TABLE II

BASAL AND MAXIMAL ACID OUTPUT IN PATIENTS AND CONTROL SUBJECTS

| Endoscopic finding | Data available | Gastric analysis | |
|---|---|---|---|
| | | BAO mEq./hr. | MAO mEq./hr. |
| 1. Visible submucosal blood vessels | | | |
| Diffuse | 4 | 0.31 ± 0.18 | 1.18 ± 0.82 |
| Circumscribed | 16 | 3.22 ± 0.88 | 15.04 ± 3.56 |
| 2. Normal mucosa | 13 | 4.01 ± 0.69 | 13.22 ± 2.71 |

Values are means ± SE

The histologic findings in this group of 25 patients and in the 26 subjects who served as controls are shown in Table I.

Atrophic gastritis was found in three of the four patients who had visible submucosal vessels that were diffusely distributed. Further investigations in these four patients established a diagnosis of pernicious anemia in two, adenocarcinoma of the stomach in one and chronic alcoholism in the other. By contrast, only one of the 26 control subjects and one of the 21 patients with circumscribed findings showed atrophic gastritis histologically.

The results of the gastric secretory study are shown in Table II. In four patients who had visible and diffusely distributed blood vessels, basal and maximal acid output were 0.31 and 1.18 mEq./hr., respectively. In 16 of those with circumscribed vascular changes and in 13 of the normal controls the same secretory values were normal without significant difference between the two groups.

## COMMENT

The endoscopic diagnosis of atrophic gastritis has been based upon the signs such as mucosal discoloration (pale gray, whitish pink or bluish),[9] mucosal smoothness and translucency[10] and visibility of submucosal blood vessels.[5] Of these endoscopic criteria, the last is popularly regarded as the hallmark of this disorder.[11]

Heinkel, utilizing suction biopsy, reported atrophic gastritis in 54.5% of the 430 patients who demonstrated the latter endoscopic sign[11] and in 48.1% of those who had smooth and translucent mucosa. Since the histologic changes are patchy,[12] it is not surprising that endoscopic and histologic correlation may not be great in studies in which a blind biopsy technic has been employed. The advent of fiberoptic endoscopy equipped with biopsy facilities has made it possible now to obtain full-thickness specimens, including the *muscularis mucosa*,[4] under direct visualization.

The data reported herein indicate that visible submucosal blood vessels may be found in as many as 13% of endoscopic examinations done on patients with symptoms referable to the upper gastrointestinal tract. Furthermore, the results of histologic examination and gastric secretory study suggest that this sign is probably a reliable index of atrophic gastritis only when distributed diffusely throughout the body and antrum, as others have also noted.[13] On the other hand, when the endoscopic findings are patchy and the vascular collections are surrounded by normal-looking mucosa, neither histologic examination nor gastric secretory study support such a diagnosis. The latter conclusion is consistent with those of Palmer and Smith[14] who found histologically normal mucosa in three of five stomachs that were endoscopically judged to show patchy gastritis.

Modern fiberoptic endoscopy provides much better light transmission and mucosal illumination. It also narrows the visual field. This makes it possible to see more details of the gastric mucosa than could be discerned with the original flexible instruments. It may well be, therefore, that the ability to see submucosal blood vessels may simply represent a gain from the improved examination and not necessarily an abnormal finding.

## CONCLUSION

Circumscribed areas in which blood vessels may be seen are found fairly often during fiberoptic gastroscopy, and such a finding does not necessarily represent atrophic gastritis. When submucosal blood vessels are visible over large reaches of the body and antrum, however, histologically confirmed atrophic gastritis is more likely to be present.

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***Communication from Abroad***

# Dye Clearance Studies in Rotor's Syndrome

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Plasma clearances of sulfobromophthalein sodium (BSP), indocyanine green (ICG) and unconjugated bilirubin were studied in six patients with Rotor's syndrome. A marked retention of these three substances in the plasma was observed. At 60 minutes after injection, serum BSP consisted almost entirely of the unconjugated form. In three patients, BSP Tm and BSP S were significantly reduced. Clearance of unconjugated bilirubin was markedly impaired. This, together with the conjugated hyperbilirubinemia may be interpreted to reflect reduced storage. These results indicate that Rotor's syndrome is marked by reduced hepatic storage capacity and excretory function of BSP, ICG and bilirubin.

Rotor's syndrome[1] is an inherited disorder characterized by conjugated hyperbilirubinemia, marked retention of sulfobromophthalein sodium (BSP), gallbladder visualization and no abnormal histological findings in the liver. It has been suggested that the syndrome may result from an inborn error in metabolism. Although considered to be closely related to the Dubin-Johnson syndrome,[2-6] these syndromes differ with respect to urinary coproporphyrin excretion.[7] We have attempted, in this study, to determine whether there is a characteristic alteration of clearance of bilirubin and of certain dyes in Rotor's syndrome in order to clarify further the features of this disorder.

## MATERIALS AND METHODS

Six patients (one female and five males) with Rotor's syndrome were hospitalized at the Hiroshima Red Cross Hospital and Kyushu University Hospital. Their mean age was 30 years with a range of 18-65 years (Table I). A familial incidence was revealed in four patients, and Cases 3 and 4 were siblings. Four of the patients had a history of persistent jaundice.

Case 3 (Y. J.) had an attack of right upper quadrant pain at age 18. At that time, intravenous cholangiography revealed common bile duct stones. He underwent cholecystectomy with common bile duct exploration but jaundice persisted. Liver biopsy at the age of 33 indicated minor

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TABLE I

CLINICAL DATA ON PATIENTS WITH ROTOR'S SYNDROME

| | Case I (O. H.) | Case 2 (T. S.) | Case 3 (Y. J.) | Case 4 (Y. H.) | Case 5 (S. M.) | Case 6 (H. K.) |
|---|---|---|---|---|---|---|
| Sex/age (yr.) | M/22 | M/19 | M/33 | F/20 | M/18 | M/65 |
| Age at onset of jaundice (yr.) | 13 | 18 | 7 | 5 | 17 | 7 |
| Familial history of jaundice | Yes | None | Yes | Yes | None | Yes |
| Past history | None | None | Cholelithiasis (18 yr.) | None | None | Pleuritis (14 yr.) |
| Alcohol intake | (–) | (–) | (–) | (–) | (–) | Seldom |
| Blood transfusion | (–) | (–) | (–) | (–) | (–) | (–) |
| Drug ingestion | (–) | (–) | (–) | (–) | (–) | (–) |
| Symptoms | Fatigability | None | None | None | None | Fatigability |
| Signs | Jaundice | Jaundice | Jaundice and hepatomegaly | Jaundice | Jaundice | Jaundice and hepatomegaly |
| Evidence of hemolysis | None | None | None | None | None | None |
| Bilirubinuria | Present | Present | Present | None | Present | Present |
| Oral cholecystogram | Normal | Normal | Cholecystectomized | Normal | Normal | Does not visualize<br>Gallstones positive |
| Liver biopsy | Normal | Normal | Minor nonspecific changes | Normal | Normal | Normal |

TABLE II

LABORATORY FINDINGS IN PATIENTS WITH ROTOR'S SYNDROME

| Test | Normal range | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|---|
| Total bilirubin (mg./dl.) | 0.2-1.0 | 6.6 | 6.4 | 12.4 | 5.0 | 4.5 | 7.9 |
| Conjugated bilirubin (mg./dl.) | < 0.4 | 5.6 | 4.5 | 10.1 | 4.0 | 3.4 | 6.2 |
| SGOT (mU./ml.) | < 40 | 36 | 13 | 57 | 8 | 15 | 22 |
| SGPT (mU./ml.) | < 40 | 24 | 22 | 60 | 5 | 15 | 18 |
| Alkaline phosphatase (K.A.[*] units) | 3-12 | 7.6 | 9.0 | 5.2 | 4.2 | 10.1 | 6.6 |
| Cholesterol (mg./dl.) | 150-300 | 155 | 160 | 240 | 220 | 183 | 177 |
| Thymol turbidity test (units) | < 4 | 1.0 | 1.7 | 1.2 | 1.0 | 0.6 | 1.9 |
| Zinc turbidity test (units) | 4-12 | 7.6 | 11.9 | 6.1 | 3.4 | 4.2 | 6.5 |
| Albumin (gm./dl.) | 3.5-5.2 | 5.2 | 4.2 | 4.3 | 5.0 | 4.8 | 3.4 |
| Gamma globulin (gm./dl.) | 0.8-1.7 | 1.2 | 1.3 | 1.0 | 0.8 | 0.8 | 1.4 |
| HBsAg |  | (−) | (−) | (−) | ND[†] | (−) | (−) |
| Anti-HBs |  | (−) | (−) | (−) | ND[†] | (−) | (−) |

[*] K.A. = King-Armstrong
[†] ND = not done

nonspecific changes with mild portal-tract infiltration and hepatocyte degeneration. There was no evidence of the dark brown, coarse pigment seen in the Dubin-Johnson syndrome. There was no history of hepatitis, chronic alcohol intake, blood transfusion, or drug ingestion.

Two of the patients were admitted because of fatigability. Signs noted included jaundice and a mild degree of hepatomegely.

Blood studies in all patients were normal and there was no evidence of excessive hemolysis. Bilirubinuria occurred in five patients. Oral cholecystography was normal in four but the gallbladder could not be visualized in Case 6. Liver biopsy specimens in five patients did not reveal any abnormal findings.

The conjugated fraction of serum bilirubin was elevated in all patients (Table II). A slight elevation in the serum transaminases was noted in one patient who had previously undergone cholecystectomy and who demonstrated minor nonspecific changes on liver biopsy. Other liver function tests were within the normal range in all six patients. HBsAg and anti-HBs were not detected in any of the patients so examined.

BSP clearance studies were carried out after an overnight fast of 12 to 14 hours. Following a single injection of 5 mg. of BSP/kg. of body weight, blood samples were obtained at 30, 45, 60, 90 and 120 minutes. Additional samples were also collected at 15 minutes (Case 6), 150 minutes (Case 1) and 240 minutes (Cases 3 and 4). BSP in plasma was determined after alkalization with 0.1N NaOH by measuring the optical density using a Hitachi spectrophotometer at 580 nm. The concentration of free and conjugated BSP in plasma was estimated in two patients at 45 and 100 minutes after the injection by the method of Combes and Stakelum.[8]

The relative hepatic storage (S) and transport maximum (Tm) of BSP were estimated by Wheeler's method.[9] After obtaining an initial blood sample, BSP was infused for one hour at a constant rate of approximately 0.15 mg./min./kg. of body weight. Four venous blood samples were drawn at 10-minute intervals during the last 30 minutes of this infusion. This procedure was repeated at infusion rates of 0.3 and 0.6 times the initial rate during the second and third hours, respectively. Plasma volume was measured in each patient using $^{131}$I-labeled human serum albumin.

Indocyanine green (ICG) clearance studies were done essentially by the method of Fauvert.[10] Blood samples were obtained in six patients at 5, 10, 15, 20, 30 and 60 minutes following a single injection of 0.5 mg. of ICG/kg. of body weight. Plasma concentration of ICG was determined spectrophotometrically at 805 nm. using 1 ml. of plasma added to 2 ml. of saline solution. The plasma disappearance rate of ICG was expressed as the percentage of the remaining dye removed per minute.

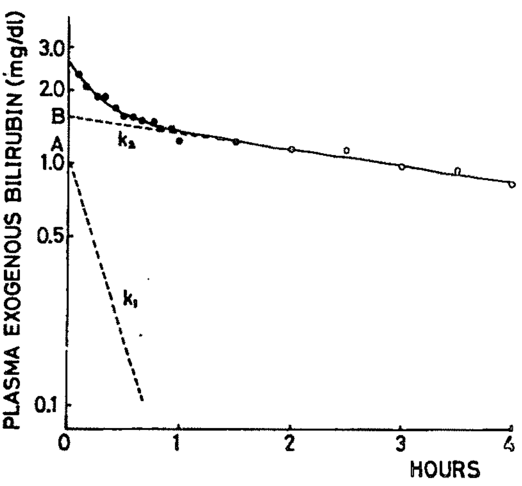

Fig. 1—Plasma disappearance curve of exogenous unconjugated bilirubin in a patient with Rotor's syndrome (Case 5). Dotted lines are individual exponential components. $k_1$ and $k_2$ are the slopes and A and B the intercepts of the two components.

Unconjugated bilirubin clearance studies were done as previously described.[11] After taking an initial blood sample, 2 mg. of unlabeled bilirubin/kg. of body weight was injected intravenously into the opposite arm and blood samples were drawn at 5-minute intervals for the first hour and subsequently every half hour up to four hours. Plasma total and direct bilirubin concentrations were determined in duplicate by Michaëlsson's method.[12] The concentration of exogenous bilirubin (EB) present in plasma at time "t" was calculated from the equation: $EB = UB - UBo$, where UB is the concentration of unconjugated bilirubin at time "t" and UBo that in the control sample. The plasma disappearance curves of exogenous bilirubin were analyzed with a digital computer curve-fitting technic. The following parameters of unconjugated bilirubin metabolism were calculated by two compartmental analyses (Fig. 1):[11, 13, 14] 1. the rate of transfer from plasma to liver, $a = Ak_1 + Bk_2/A + B$; 2. the rate of reflux from liver to plasma, $b = (k_1 + k_2) - (a + m)$; the rate of transfer from unconjugated to conjugated bilirubin, $m = k_1 \times k_2/a$ and the percentage retention at four hours, % retention = EB4hr./ EBo × 100. The bilirubin extraction coefficient

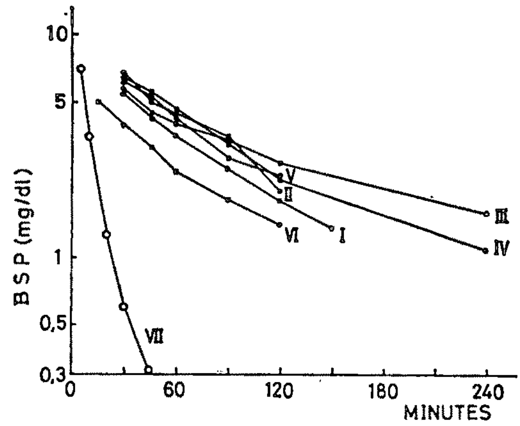

Fig. 2—BSP disappearance curve after single injection (5 mg./kg.) The changes in serum concentration of BSP with time are shown for six patients with Rotor's syndrome and seven normal subjects. Case 1 (I), 2(II), 3(III), 4(IV), 5(V), 6(VI), and normal subjects (VII).

(Ke) and bilirubin clearance (CBR) were calculated by the following formulas:

$$\mathrm{Ke} = \frac{\mathrm{a} \times \mathrm{m}}{\mathrm{b} + \mathrm{m}}$$

$$\mathrm{CBR} = \mathrm{Ke} \times \mathrm{VDBR}$$

where the volume of distribution of bilirubin (VDBR) was calculated from

$$\mathrm{VDBR} = \frac{\text{injected dose (mg.)}}{\text{mg./ml. plasma at } t_0}$$

The following tests were performed on each patient using standard procedures: SGOT, SGPT, alkaline phosphatase, cholesterol, thymol turbidity, zinc sulfate turbidity and electrophoresis of serum proteins. HBsAg was tested by both counterelectrophoresis[15] and reversed passive hemagglutination[16] and anti-HBs by passive hemagglutination.[17]

Statistical analysis was made by Student's "t" test.

## RESULTS

Results of the plasma disappearance curves of BSP are shown in Figure 2 and Table III. There was a marked retention of BSP as compared to seven normal subjects; BSP retention at 45 minutes was 46 ± 8% (mean ± SD) vs. 3 ± 2%, respectively ($P < 0.01$). The late rise in BSP, as seen in Dubin-Johnson syndrome, was not found. BSP Tm and BSP S in three patients with Rotor's syndrome were 3.2 ± 0.6 mg./min. (mean ± SD) and 20 ± 4 mg./mg./dl., respectively. These values were significantly reduced ($P < 0.01$) compared to the reference values of 5.7 ± 1.5 mg./min. and 73 ± 26 mg./mg./dl. obtained from 11 Japanese controls.[18] Plasma disappearance rates of ICG in seven normal subjects and six patients with Rotor's syndrome were 19.6 ± 3.4 and 3.2 ± 1.2%/min., respectively (Table III). The difference between these two groups was highly significant ($P < 0.01$). The late rise in ICG or BSP did not occur. The concentration of free and conjugated BSP was estimated in plasma obtained in two patients at 45 and 100 minutes after injection of the dye. The percentages of free BSP at these time periods in Case 3 were 98.6 and 97.4%, respectively and those in Case 4 were similar (Table IV).

The plasma disappearance curve of exogenous bilirubin in one patient (Case 5) with Rotor's syndrome was fitted by the sum of two exponential function (Fig. 1). The clearance of unconjugated bilirubin was more markedly reduced in Rotor's syndrome than in normal subjects. With respect to the parameters examined, "a", "b", "m", Ke and CBR in seven normal subjects were 0.0294 ± 0.0032 (mean ± SD), 0.0139 ± 0.0028, 0.0145 ± 0.0041, 0.0148 ± 0.0026 and 56 ± 10 ml./min., respectively (Table V). The results of studies in two patients with Rotor's syndrome showed that the lower Ke and CBR values were associated with a slight decrease in a, 0.0217 vs. 0.0225, a moderate increase in b, 0.0259

TABLE III

DYE CLEARANCE STUDIES IN PATIENTS WITH ROTOR'S SYNDROME

| Case no. | BSP retention (%, 45 min.) | BSP Tm (mg./min.) | BSPS (mg./mg./dl.) | Plasma disappearance rate of ICG (%/min.) |
|---|---|---|---|---|
| 1 | 43 | Not estimated | | 4.1 |
| 2 | 50 | Not estimated | | 2.8 |
| 3 | 44 | 2.7 | 16 | 4.6 |
| 4 | 55 | 3.1 | 24 | 3.9 |
| 5 | 52 | 3.8 | 19 | 1.7 |
| 6 | 33 | Not estimated | | 2.0 |
| Mean ± SD | 46 ± 8 | 3.2 ± 0.6 | 20 ± 4 | 3.2 ± 1.2 |
| Normal range (Mean ± SD) | 3 ± 2(7)* | 5.7 ± 1.5(11) | 73 ± 26(11) | 19.6 ± 3.4(7) |

* Figures in parentheses denote the number of normal controls

vs. 0.0269 and a significant decrease in m, 0.0034 vs. 0.0068.

## COMMENT

Rotor, et al[1] in 1948 described a type of familial disorder characterized by chronic nonhemolytic, predominantly conjugated hyperbilirubinemia. In contrast to the Dubin-Johnson syndrome, no pigment is present in the liver cells and oral cholecystography is frequently normal in spite of increased BSP retention. Although it has been suggested that Rotor's syndrome may be closely related to the Dubin-Johnson syndrome,[2-6] both syndromes are distinct pathophysiologic entities with respect to urinary coproporphyrin excretion.[7]

Our six patients with Rotor's syndrome showed persistent jaundice with or without a mild degree of hepatomegaly. Serum bilirubin concentration was less than 13 mg./dl. and predominantly conjugated. There was no clear-cut correlation, however, between age at the time jaundice was detected and serum bilirubin concentration.

Five patients were repeatedly tested for HBsAg and anti-HBs after the onset of jaundice and were found to be negative. Gallbladder visualization was normal in all cases, suggesting that iopanoic acid used as contrast material does not share hepatic transport pathways with BSP and bilirubin. Histologic examinations of liver biopsies were normal in five of the patients; one biopsy (Case 3) showed minor nonspecific changes.

Two important diagnostic features were noted in dye clearance studies of the patients with Rotor's syndrome. First was a marked retention of BSP and a striking reduction in the plasma disappearance rate of ICG. BSP bound to albumin is transported to the liver where the dye is conjugated with glutathione and excreted into the bile. ICG bound to serum proteins is similarly taken up by the liver but excreted unchanged into the bile. Therefore, it

TABLE IV

ANALYSIS OF BSP IN SERUM FROM PATIENTS WITH ROTOR'S SYNDROME

| | Case 3 | | Case 4 | |
|---|---|---|---|---|
| Time after injection (min.) | 45 | 100 | 45 | 100 |
| BSP (mg./dl.) | 4.3 | 2.9 | 5.0 | 3.0 |
| Conjugated BSP (%) | 1.4 | 2.6 | 1.3 | 3.2 |
| Free BSP (%) | 98.6 | 97.4 | 98.7 | 96.8 |

seems likely that in Rotor's syndrome there is disordered hepatic excretion of organic anions such as BSP and ICG. The second diagnostic feature was that despite marked retention of BSP or ICG, a late rise in BSP or ICG was not detected. Mandema, et al[19] found that there was a late rise in BSP in Dubin-Johnson syndrome, probably through re-entry of some of the conjugated BSP from the liver cells into the blood stream. The results of the present study suggest that the absence of late rise in BSP might be helpful in differentiating Rotor's syndrome from Dubin-Johnson syndrome.

BSP in the serum at 45 and 60 minutes after intravenous injection of BSP proved to be overwhelmingly of the free form. According to Wolpert, et al[20] and from our results, BSP Tm and BSP S are significantly reduced compared to normal subjects. It seems reasonable, therefore, to consider that patients with the Rotor syndrome have decreased hepatic BSP uptake and storage. Hepatic excretory function of BSP is similarly disturbed. By contrast, BSP Tm in Dubin-Johnson syndrome is virtually zero, whereas BSP S is within the normal range.[9, 18, 21] Thus, this disorder involves a specific excretory defect in the ability to transport BSP and other organic anions from the liver cells to the bile.[22, 23] The data in this study indicate that the

TABLE V

KINETICS OF PLASMA UNCONJUGATED BILIRUBIN CLEARANCE IN NORMAL SUBJECTS AND PATIENTS WITH ROTOR'S SYNDROME*

| | No. of cases | Transfer rate constants (mg. bilirubin/mg. content/min.) | | | Ke (min.-1) | $C_{BR}$ (ml./min.) | % retention at 4 hours |
|---|---|---|---|---|---|---|---|
| | | a | b | m | | | |
| Normal subjects | 7 | 0.0294<br>± 0.0032 | 0.0139<br>± 0.0028 | 0.0145<br>± 0.0041 | 0.0148<br>± 0.0026 | 56<br>± 10 | 9<br>± 3 |
| Rotor's syndrome | 2 | | | | | | |
| Case 2 | | 0.0217 | 0.0259 | 0.0034 | 0.0025 | 13 | 43 |
| Case 5 | | 0.0225 | 0.0269 | 0.0068 | 0.0045 | 23 | 34 |

* Values are mean ± SD

dye clearance is by far the most important factor for differentiating Rotor's syndrome from Dubin-Johnson syndrome. As described by Wolpert, et al,[20] both syndromes are distinct entities with respect to dye metabolism and transport.

The clearance of unconjugated bilirubin from the plasma was also markedly impaired in Rotor's syndrome. In fact, two compartmental analysis suggested that both hepatic uptake of unconjugated bilirubin from plasma and hepatic conjugation were diminished. By contrast the rate of reflux from liver to plasma was increased. Since two significant biological parameters, Ke and CBR, do not depend on any particular model,[13, 24] it may be concluded that marked retention of unconjugated bilirubin is responsible for the unequivocal decrease in bilirubin clearance. One possible explanation for this phenomenon may be the fact that the liver has decreased capacity to store the bilirubin removed from the plasma and to excrete bilirubin into the bile as in the case when BSP S and BSP Tm are decreased. Previous studies on Rotor's syndrome,[2, 14] however, suggested a defect in the secretion of conjugated bilirubin as is seen in Dubin-Johnson syndrome. To determine the true mechanism, further detailed examination using radiobilirubin should be conducted.

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*Communication from Abroad*

# Effect of Phenoxybenzamine (POB) on Portal Venous Pressure in Patients with Portal Hypertension

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In order to assess an effect of phenoxybenzamine (POB) on portal circulation, POB (0.5-1.0 mg./kg.) was administered intravenously to six patients with portal hypertension and two patients without portal hypertension. In patients with portal hypertension, POB reduced portal venous pressure (PVP) from 362.5 ± 53.8 mm. $H_2O$ to 282.5 ± 50.4 mm. $H_2O$ ($P < 0.001$) where central venous pressure (CVP) was maintained constant. In patients without portal hypertension, change in PVP was in parallel with that in CVP where the decrease in PVP was regarded as not specific. This preferential reduction of PVP in portal hypertension seemed to implicate functional vasoconstriction of the portal venous system. In the treatment of bleeding esophageal varices, use of POB with blood transfusion after decompression of the Sengstaken-Blakemore tube should be beneficial because of its prolonged effect of lowering PVP and preventing ischemic liver damage.

Phenoxybenzamine (POB) is known to be an effective adrenergic receptor blocking agent. It has not been used extensively, however, by clinicians because of its powerful potency and also because its prolonged action is difficult to control. It has a potent peripheral vasodilator effect as a result of the relief of sympathetic vasoconstriction. Knowledge of this effect led to the idea to apply POB in the treatment of peripheral vascular insufficiency especially when associated with shock.[1] Administration of POB into extracorporeal circulation during open-heart surgery for the prevention of subsequent low cardiac output syndrome was first proposed by Lillehei, et al.[2] It is also useful as a diagnostic agent for pheochromocytoma. Prophylactic effect was observed in patients with Printzmetal's variant form of angina.[3] Therefore POB has been used for the treatment of a variety of conditions.

Recently Ohta, et al observed that POB produced significant reduction of pulmonary vascular resistance in patients with pulmonary hypertension.[4] Because regional hypertensive changes occur in portal hypertension, it was decided to evaluate the value of POB in this condition.

## PATIENTS AND METHODS

The study was performed on six patients, (one male and five females, average age 47 years) with portal hypertension (Table I). The etiology of their portal hypertension was liver fibrosis (5) and portal thrombosis (1). All six patients developed splenomegaly and esophageal varices and underwent splenectomy, devascularization of the stomach and eventually esophageal transection. Two patients with anemia but no hypertension were included in the study (Table II).

All the patients were anesthetized with GOF. Respiration was controlled and ar-

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TABLE I

PRESSURE MEASUREMENTS IN PATIENTS WITH PORTAL HYPERTENSION FOLLOWING INFUSION OF PHENOXYBENZAMINE (POB)

| Patients | Disease | Pressure | Before POB | After POB | Pressure gradient | After splenectomy | Weight of spleen (gm.) |
|---|---|---|---|---|---|---|---|
| 40 F | Liver fibrosis | PVP (mm. $H_2O$) | 400 | 350 | − 50 | 320 | 930 |
| | | BP (mm.Hg.) | 130/90 | 120/80 | | 90/60 | |
| | | CVP (mm. $H_2O$) | 80 | 85 | + 5 | 85 | |
| 48 F | Thrombosis of portal vein | PVP | 325 | 225 | − 100 | 200 | 1,000 |
| | | BP | 100/60 | 80/40 | | 90/60 | |
| | | CVP | 105 | 115 | + 10 | 105 | |
| 50 F | Liver fibrosis | PVP | 280 | 220 | − 60 | 170 | 850 |
| | | BP | 140/90 | 95/50 | | 110/80 | |
| | | CVP | 75 | 75 | 0 | 80 | |
| 62 F | Liver fibrosis | PVP | 400 | 300 | − 100 | 250 | 500 |
| | | BP | 120/80 | 120/60 | | 80/50 | |
| | | CVP | 60 | 100 | + 40 | 60 | |
| 42 M | Liver fibrosis | PVP | 420 | 300 | − 120 | 250 | 800 |
| | | BP | 130/80 | 110/70 | | 110/70 | |
| | | CVP | 80 | 90 | + 10 | 90 | |
| 38 F | Liver fibrosis | PVP | 350 | 300 | − 50 | 260 | 750 |
| | | BP | 120/80 | 110/70 | | 100/60 | |
| | | CVP | 90 | 90 | 0 | 90 | |
| | PVP (mean ± SD) | | 362.5 ± 53.8 | 282.5 ± 50.4 | 80.0 ± 30.3 | | |
| | CVP (mean ± SD) | | 81.7 ± 15.1 | 92.5 ± 13.7 | 10.8 ± 15.0 | | |

PVP = portal venous pressure; BP = systemic arterial pressure;
CVP = central venous pressure.

terial $Pco_2$ and pH were maintained at 30-35 mm. Hg. and 7.30-7.35 respectively during the operation. Cubital arterial pressure was measured by sphygmomanometer. A branch of the superior mesenteric vein was cannulated with a polyvinyl catheter into the portal vein for monitoring portal venous pressure (PVP). Similarly, central venous pressure (CVP) was monitored through a cannula in the thoracic portion of the inferior vena cava via the saphenous vein. The position of the cannula was confirmed by roentgenogram of the chest. The patients' mid axillarly line was taken as 0 level of both pressures. Portal collateral channels were demonstrated in the retroperitoneum and paraesophagogastric area by angiographies from the mesenteric vein and the spleen, in all cases with hypertension.

After the pressure in three vessels was measured, POB (Nikken Chem. Co.) in the dose of 0.5-1.0 mg./kg., dissolved in 500 ml. of 5% glucose solution was infused into the cubital vein in 15-30 minutes. CVP was measured every five minutes and maintained as constant as possible by blood transfusion, when required. PVP was measured before and after POB administration and before and after splenectomy.

Statistical analyses were performed using the Students' "t" test for paired data.

## Results

Hemodynamic changes following POB administration are summarized in Tables I and II. In portal hypertension, PVP ranged from 420 to 280 mm. $H_2O$ (mean ± SD 362.5 ± 53.8 mm. $H_2O$). When POB was infused, marked reduction of PVP to the mean value of 282.5 ± 50.4 mm. $H_2O$ (77.9% of the original value) was observed ($P < 0.001$). A typical example of this for a 62-year old female is seen in Figure 1. CVP was maintained almost

TABLE II

Pressure Measurements in Patients withoht Portal Hypertension Following Infusion of Phenoxybenzamine (POB)

| Patients | Disease | Pressure | Before POB | After POB | Pressure gradient | After splenectomy | Weight of spleen (gm.) |
|---|---|---|---|---|---|---|---|
| 33 F | Idiopathic thrombopenic purpura | PVP (mm. $H_2O$) | 160 | 175 | + 15 | 155 | 300 |
| | | BP (mm.Hg.) | 140/90 | 120/70 | | 110/60 | |
| | | CVP (mm. $H_2O$) | 110 | 120 | + 10 | 105 | |
| 35 F | Aplastic anemia | PVP | 145 | 135 | − 10 | 130 | 150 |
| | | BP | 130/90 | 120/70 | | 120/70 | |
| | | CVP | 100 | 90 | − 10 | 90 | |

PVP = portal venous pressure; BP = systemic arterial pressure;
CVP = central venous pressure.

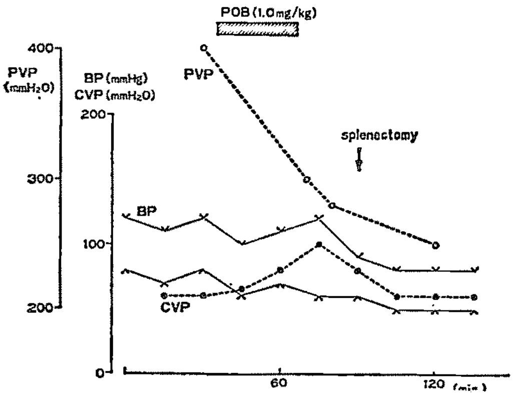

Fig. 1—The effect of administration of phenoxybenzamine (POB, 1.0 mg./kg.) on portal venous (PVP), systemic arterial (BP) and central venous (CVP) pressures in a 62-year old female with liver fibrosis.

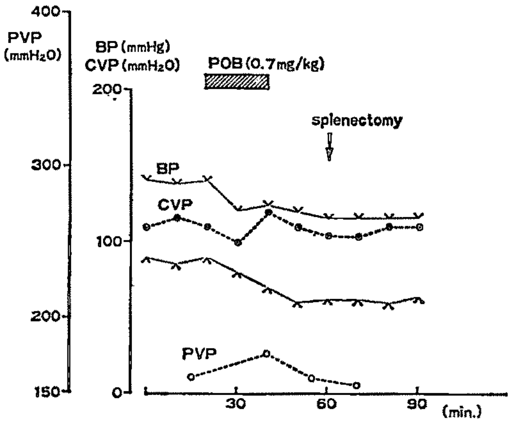

Fig. 2—The effect of administration of phenoxybenzamine (POB, 0.7 mg./kg.) on portal venous (PVP), systemic arterial (BP) and central venous (CVP) pressures in a 33-year old female with idiopathic thrombopenic purpura.

constant or slightly elevated by rapid infusion of POB-glucose solution or additional blood transfusion. In spite of the increase in circulating blood volume, both systolic and diastolic pressure were depressed following POB administration, reflecting a decrease in peripheral vascular resistance. There was no significant change in heart rate following POB, although the effect of premedicated atropine sulfate cannot be disregarded. After splenectomy, PVP was reduced to 60-80% of the original level. The extent of reduction in PVP was unrelated to the weight of extirpated spleen.

In cases without portal hypertension (less than 200 mm. $H_2O$) where only splenectomy was performed, peripheral vascular resistance also decreased following POB. Change in PVP, however, was in parallel with that in CVP (Fig. 2). Decrease in PVP after splenectomy was less than 11%.

## Comment

Since 1947 when Nickerson and Goodman discovered that dibenamine could block the alpha adrenergic receptor,[5] some 1,500 beta halokylamine compounds have been synthesized and tested, except for POB.[6] POB produces a decrease in total peripheral vascular resistance but its effect seems to vary with vascular beds of different locations. Cerebral and coronary resistance are not altered significantly by POB.[7] The recommended blocking dose (1 mg./kg.) of POB induced reduction in pulmonary arterial pressure in patients with pulmonary hypertension, which was greater than that produced in normotensive subjects.[4]

In patients with portal hypertension, intravenous infusion of POB (0.5-1.0 mg./kg.) induced remarkable reduction of PVP where CVP was maintained constant. On the other hand in patients without hypertension, change in PVP paralleled that in CVP. Since vasodilatation from POB may vary in different arterial beds, two possibilities can be considered: the fall in portal pressure is due simply to reduced arterial inflow to the portal bed or to reduced vascular resistance in the liver and/or portal collateral channels. Although hepatic blood flow was not measured, the former seems to be unlikely. If the splanchnic vasodilatation is less than the vasodilatation elsewhere, then splanchnic blood flow would decrease as systemic arterial pressure falls. In the Case 1 of Table II, however, PVP increased (as CVP increased), while systemic arterial pressure fell after POB. Thus, preferential reduction of PVP in patients with portal hypertension seems to implicate functional vasoconstriction of the portal venous system. Effects of catecholamines on canine portal pressure are found secondary to contraction of the spleen as well as constriction of portal vein.[8] This evidence is also favorable to the view that disturbance in catecholamine metabolism is one of the etiologic factors for portal hypertension.[9] What part of the portal venous system, however, would participate in developing hypertension is unknown. Responsiveness of the portasystemic venous collaterals to POB is also unknown.

Intravenous administration of vasopressin was applied for the control of hemorrhage from esophageal varices.[10, 11] Clinical success has been achieved with selective infusion of vasopressin into the superior mesenteric artery in the treatment of ruptured esophageal varices.[12] The use of vasopressin is based on the evidence that it reduces mesenteric blood flow by constricting mesenteric arterioles.[13, 14] Although the action is relatively specific and hepatic arterial flow is affected only slightly,[15] vasopressin is essentially a vasoconstrictive agent and is relatively slowly metabolized as compared with epinephrine.[16] Therefore it must be anticipated that excessive or repeated administration would induce ischemic liver damage. Moreover, in patients with ascites, the possibility should be taken into account that antidiuretic effect of vasoconstrictive agent may induce retention of ascites. On the other hand, under normovolemic condition, the vasodilating effect of POB in hepatic[8] and renal[17] circulation would increase blood flow to both organs and diuresis. Pretreatment with POB appeared to be of benefit in retarding the onset and lessening the severity of hepatocellular injury after hepatic ischemia.[18]

When the circulating blood volume is within physiological range, CVP changes in parallel with pulmonary arterial pressure and left atrial pressure. Therefore, fluctuation of CVP reflects closely an alteration of circulating blood volume unless serious shock or cardiac insufficiency coexists. Also in patients with portal hypertension, unless there is circulatory complication such as right heart insufficiency or obstruction of the vena cava, monitoring CVP is very useful for estimation of circulating blood volume and is a safeguard especially for the use of POB.

The Sengstaken-Blakemore double balloon tube is one of the most reliable means in controlling bleeding from esophageal varices. If, however, PVP remains high and untreated, recovery of systemic hypotension by blood transfusion will often bring about rebleeding after decompression of the balloon. Combined use of POB with blood transfusion would be favorable because of its prolonged effect of lowering PVP and increasing hepatic arterial flow in any situation involving sympathetic vasoconstriction.

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*Clinical Vignette*

# Esophagitis Caused by *Torulopsis Glabrata*

## CASE REPORT

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## INTRODUCTION

"Monilial" esophagitis is a disease generally affecting the host compromised by debilitating illness or chronic use of broad-spectrum antibiotics or chemotherapeutic agents. It may rarely be seen in individuals with none of these predisposing factors.[1] Various *Candida* species have been shown to be the causative agents, but one individual has been reported to have esophagitis due to *Torulopsis glabrata.*[2] We recently saw a patient who had clinical findings consistent with "monilial" esophagitis where *Torulopsis glabrata* was the only organism isolated from esophagoscopy specimens.

## CASE REPORT

A 63-year old white man was admitted to St. Luke's Episcopal Hospital for treatment of injuries suffered when he fell off a stool during an apparent grand mal seizure. There was no previous history of a seizure disorder or other neurologic disease. Forty-five years prior to admission, his right leg was amputated above the knee because of complications following two previous operations for a sports injury. He suffered myocardial infarctions 24 and 22 years prior to admission. He had surgery again in 1960 and 1961 for placement and removal of a pin in the right proximal femur. Three years prior to admission, he received radiation therapy for moderately well-differentiated squamous cell carcinoma of the true vocal cord. He had been taking an antacid for indigestion. There was no history of diabetes mellitus or recent use of antibiotics or chemotherapeutic agents.

Physical examination disclosed a well-developed, well-nourished white man in acute distress. Because of an irregular pulse rate and symptoms of congestive heart failure, he was admitted to the intensive care unit with a presumptive diagnosis of Stokes-Adams attack. Fractures of the right hip, left humerus and 12th thoracic vertebral body were present on x-ray. Electrocardiogram showed bundle branch block, premature atrial contractions and first degree atrioventricular block. White blood cell count was 14,000/cu. mm. and other routine laboratory data were unremarkable.

On the fifth hospital day, the patient experienced projectile vomiting and abdominal distention with mild abdominal tenderness and decreased bowel sounds. A roentgenogram of the abdomen revealed increased gas in the small bowel and transverse colon. Nasogastric suction was initiated. On the seventh hospital day, his clinical status had improved with some decrease in the amount of abdominal distention. Decompression of the bowel was attempted with enemas, rectal tube and continued nasogastric suction. Later that day, bright red blood was noted in the nasogastric tube. Barium enema done the following day revealed a small bowel ileus with distention of the cecum and transverse colon. On the ninth hospital day, esophagogastroscopy was performed. White, irritative lesions extending from the mid point of the esophagus down to the gastroesophageal junction were noted. There were also irritative lesions in the distal stomach. Cultures from the esophagus grew *Torulopsis glabrata* but no *Candida* species. Cultures taken from a rash on the patient's back grew only normal skin bacteria. The patient was started on Mycostatin and an antacid alternately every two hours per nasogastric tube. Mycostatin cream was applied to the back rash. After transfusion of 2 units of packed red blood cells, the patient's clinical condition gradually improved. Nasogastric suction was discontinued on the 15th hospital day after bright red blood was again seen in the nasogastric tube. That same day, the patient suffered a respiratory arrest but was promptly resuscitated. A barium swallow performed on the 21st hospital day showed no abnormalities except for a sliding hiatal hernia. Repeat esophagoscopy showed the irritative lesions to be much improved and no fungus was isolated from the brushing specimens.

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The remaining period of recovery was uneventful except for a second seizure and an episode of epididymitis which resolved on Ampicillin. Mycostatin was continued until the day of discharge, the 66th hospital day.

## COMMENT

"Monilial" esophagitis occurs in a wide variety of clinical situations. Cancer patients receiving immunosuppressive drugs make up the greatest percentage of reports of "monilial" esophagitis in the literature.[2-6] Other patients on long-term steroid[3, 5, 7] or antibiotic[4, 5, 7, 8] therapy have been reported to develop candidal infections of the esophagus. Diabetics[5, 8] may also be predisposed to this affliction. There are reports of individual cases of candidal esophagitis in patients with aplastic anemia, pancytopenia secondary to disseminated tuberculosis, Parkinson's disease, alcoholism,[4] hemoglobin SC disease,[9] extensive burns[10] and peptic ulcer disease.[11] One report links prior surgery to *Candida albicans* sepsis.[12] There is only one case in the literature, however, of "monilial" esophagitis caused by *Torulopsis glabrata*. This was included in a group of 35 cancer patients with "monilial" esophagitis.

*Torulopsis glabrata* is a fungus closely related to the *Candida* genus that was generally considered to be nonpathogenic until the report by Wickerham in 1957 clearly documented its potential for causing disease.[13] The first mention in the literature of *T. glabrata* infection was the 1937 report of a ten-year old child with bronchopneumonia where the organism was cultured from the sputum.[14] In 1950, *T. glabrata* was isolated from the uterus and fallopian tube of a female with granulomatous lesions of the reproductive organs.[15] More recently, urinary tract infections[16-18] and sepsis[16, 19-22] have been found to be caused by *T. glabrata*. In all of these patients, some predisposing factor for opportunistic infection was present.

The case presented here is the second instance reported in the literature of esophagitis caused by *Torulopsis glabrata*. It is not clear whether this is indicative of the rarity of the disease or merely a lack of proper identification of the causative organism in all cases of "monilial" esophagitis. This patient probably had several predisposing factors for opportunistic infection. It is likely that, with a history of "indigestion", he may have had mild gastritis or reflux esophagitis. There was a history of malignant disease but no evidence of recurrence was found at the time of this hospitalization. Because of the absence of persistent arrhythmias in the face of continuing seizure activity, it was felt that he was not experiencing Stokes-Adams attacks, although a period of hypotension might result in increased vulnerability to infection. We could find no reports in the literature of "monilial" esophagitis associated with an idiopathic seizure disorder. It may be conjectured, however, that his congestive heart failure played a role in the evolution of the esophagitis by causing diminished peripheral perfusion. It is doubtful that multiple surgical procedures occurring many years previously could still be a factor in the lowering of host defenses. The cause of the intestinal obstruction in this patient is unclear, but it may have been due to a local volvulus secondary to traumatic ileus. Regardless of the nature of the predisposing factors in this case, it is evident that *Torulopsis glabrata* is a potential pathogen and can cause a clinical picture identical to that seen in candidal esophagitis.

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***Clinical Vignette***

# Endoscopic Resection of Squamous Papilloma of the Esophagus

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Squamous papilloma is a rare, benign esophageal tumor which may be confused with verrucous carcinoma of the esophagus. The case of a 45-year old male who was found to have an esophageal squamous papilloma is presented. This case serves to demonstrate the important role of fiberoptic endoscopy for the transendoscopic resection of this tumor.

Squamous papilloma of the esophagus is a rare, benign esophageal tumor.[1] Only a few cases of esophageal papilloma have been verified endoscopically and even fewer cases have been confirmed by biopsy at the time of endoscopy.[1-3] The endoscopic resection of an esophageal papilloma has been reported only once previously during the era of fiberoptic endoscopy.[3] The case of a patient who had a squamous papilloma of the distal esophagus which was verified and resected endoscopically constitutes the subject of this report.

## CASE REPORT

A 45-year old executive was seen in May, 1976, for evaluation of an esophageal lesion. One month earlier, he underwent a routine medical evaluation. He was asymptomatic and his physical examination was normal. Roentgenograms of the upper gastrointestinal tract, performed as a part of his evaluation, revealed a circumscribed 0.7 cm. in diameter, filling defect in the distal esophagus proximal to the esophagogastric junction (Fig. 1). Endoscopic examination demonstrated the presence of a soft, papillary erythematous lesion. The remainder of the examination was normal. The lesion was resected transendoscopically, and was histologically demonstrated to be a squamous papilloma. Adjacent esophageal tissue showed minimal chronic inflammation. No evidence of malignancy or atypia was evident either in the papilloma or in the adjacent tissue.

The patient has remained asymptomatic. Periodic roentgenographic re-evaluation performed at three- to four-month intervals over an 11-month period after resection has shown a normal esophagus with no evidence of the previous lesion (Fig. 2).

## COMMENT

Although common in most squamous epithelial surfaces, the squamous papilloma is a distinct rarity in the esophagus.[1, 4] In 1957, Stout and Lattes raised serious doubts as to the existence of esophageal papilloma as a clinical entity.[4] They claimed to have found no bona fide example of a papilloma among cases previously reported and suggested that the nature of the lesion was inflammatory rather than papillomatous. In 1959, Adler, et al, reported the surgical resection and histologic verification of an

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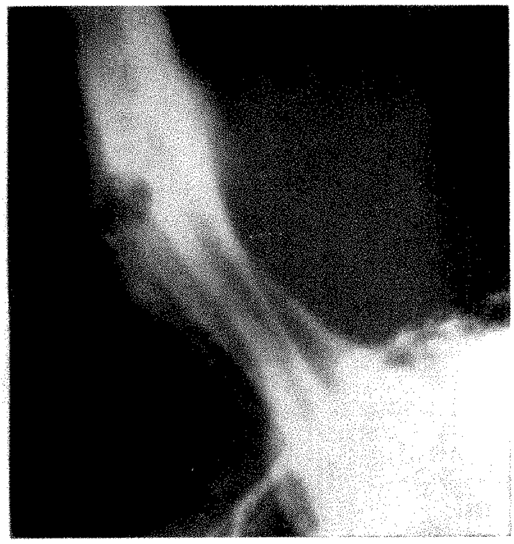

Fig. 1—Esophagogram at the time of diagnosis, showing a polypoid circumscribed lesion in the distal esophagus.

esophageal papilloma.[5] Since then, three more cases of histologically confirmed esophageal papilloma have been reported.[1-3]

The etiology of the esophageal papilloma remains unknown. It has been suggested that chemical or viral agents and/or mechanical factors may contribute to the pathogenesis of similar lesions in animals.[6] No overt evidence of specific etiologic factors has been noted either in our patient or in previously reported cases. Papillomas are usually asymptomatic,[1-3, 5] however, most patients have symptoms related to concurrent gastroesophageal conditions which lead to clinical investigation and discovery of a papilloma.[2, 3, 5]

Esophageal papillomas may be single or multiple in number. They are usually small in size, measuring anywhere from 0.4-1.5 cm. in greatest length.[1-3, 5] Although their most frequent location is the middle or distal third of the esophagus, one case of multiple papillomas of the upper third of the esophagus has been reported.[1-3, 5] Our patient had a single lesion measuring 0.7 cm. in greatest length which was located in the distal esophagus.

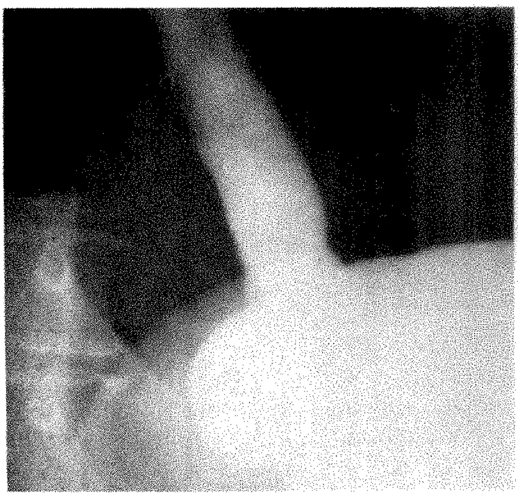

Fig. 2—The distal esophagus shows no evidence of recurrence of the papilloma 11 months after endoscopic resection.

It is important to confirm the diagnosis of esophageal papilloma histologically since this lesion may be confused with verrucous carcinoma of the esophagus on visual inspection. Endoscopy with biopsy provides a suitable means of obtaining tissue for histologic identification. Of four cases of papilloma reported since 1959, endoscopy was employed in two cases and provided histologic verification of the papilloma.[2, 3] Furthermore, in this era of therapeutic endoscopy, esophagoscopy also provides a relatively safe and simple route for resection of the papilloma. We are aware of only one case of endoscopic resection of a papilloma that has been reported in the era of fiberoptic endoscopy. Benisch and Mantell[3] resected endoscopically three papillomas from the distal esophagus of a 58-year old man. Although these authors do not mention the type of endoscope they used, the papilloma from the distal esophagus of our patient was resected through a flexible fiberoptic panendoscope. The success of endoscopic resection in both patients is further attested to by the absence of recurrence in our patient and in the case of Benisch and Mantell, 11 and 14 months, respectively, after resection.

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***Clinical Vignette***

# Granular Cell Tumor of the Common Bile Duct

## CASE REPORT AND REVIEW OF LITERATURE

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A case of granular cell tumor is reported and the main features of the previously reported cases are summarized. This lesion usually presents in a black woman as a small tumor obstructing the common bile duct and resulting in cholecystitis and/or obstructive jaundice. The cell of origin is still disputed. Local resection with cholecystectomy and choledochoduodenostomy appears to be the treatment of choice.

Granular cell tumor is an uncommon neoplasm of soft tissue. This entity has been described in several different anatomic sites which include the oral cavity,[1] skin,[1] gastrointestinal tract,[2] breast,[3, 4] biliary system,[5, 6] respiratory system,[7] pituitary,[8, 9] female reproductive organs,[10] orbit,[1] mastoid region.[1] The commonest site is the tongue.[1] Granular cell tumor is uncommon in the biliary system; only 15 cases have been reported thus far and six of these cases were located in the common bile duct. It is therefore the purpose of this communication to describe an additional case in this location and to summarize the salient clinical and pathological features of this tumor when it occurs in the common duct.

## CASE REPORT

E. S., a 46-year old black female was admitted to the Martland Medical Center complaining of right-sided abdominal pain of three weeks duration. The pain was constant, nonradiating and localized in the right upper quadrant. It was not associated with food ingestion and the patient vomited clear fluid once on the day prior to admission. She gave no history of fatty food intolerance, hematemesis, melena, weight loss or changes in either stool color or bowel habits. She had been admitted to the hospital three months ago for similar complaints when gastrointestinal contrast

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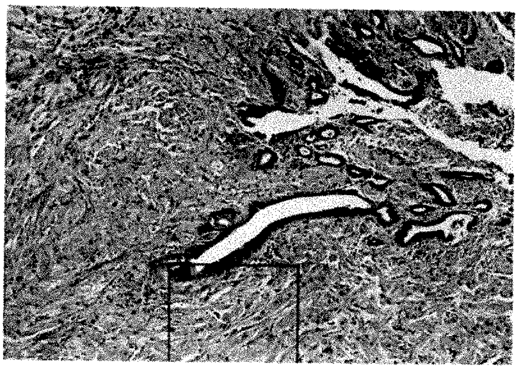

Fig. 1—Section through thickened common duct. Note bile duct epithelium at center and right. Thickening of wall is due to proliferation of granular cells (Hematoxylin and eosin, original magnification x235).

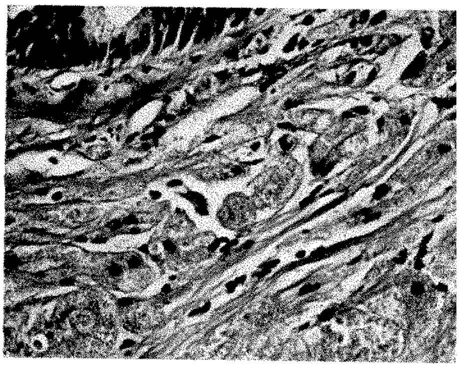

Fig. 2—Detail of area, in box from Fig shows pale granular cells with distin borders and small uniform nuclei ( toxylin and eosin, original magnifi x900).

studies, intravenous urography and liver biopsy were normal. Esophagogastroscopy revealed squamous cell dysplasia of the distal third of the esophagus but no evidence of carcinoma. She then left the hospital before an oral cholecystogram could be performed. Physical examination revealed a well nourished middle aged woman in moderate distress. Her blood pressure was 110/70 mm./Hg.; temperature, 37° C and pulse 80/min. Relevant physical findings were confined to the abdomen. There was no distention and bowel sounds were normal. Tenderness, guarding and a positive Murphy's sign were elicited in the right upper quadrant. Laboratory investigations, consisting of a complete blood count, serum electrolytes, blood sugar, blood urea nitrogen, serum bilirubin, liver enzymes, amylase and urinalysis were all within normal limits. Roentgenograms of the chest and abdomen were also normal. The gallbladder was not visualized by oral cholecystography on two occasions.

The patient was treated with nasogastric suction and intravenous fluids with the provisional diagnosis of acute cholecystitis. Since she failed to improve, a laparotomy was advised eight days following admission.

Exploration of the abdomen revea shrunken, fibrotic gallbladder. The com duct was enlarged and felt fibrotic. A c cystectomy was performed and an i operative cholangiogram showed obs tion of the common duct just distal t cystic duct.

The duodenum was kocherized a duodenotomy was performed. The am of Vater was identified but retrograde nulation of the common duct was not cessful. The common duct was divided a specimen was submitted for frozen tion. The common duct was excised al the cystic duct, leaving a patent com hepatic duct which was anastomosed t duodenum. The common duct stump oversewn. A red rubber catheter was ized as a stent and brought out throug duodenal wall and connected to a drai bag.

The patient pursued a benign operative course till one week post atively when the stent was inadvert removed. She was followed carefully two weeks but remained asymptomatic a normal serum bilirubin.

## PATHOLOGY

A segment of common duct which had a greatly thickened wall and markedly narrowed lumen was submitted for frozen section. Histologically there was marked fibrous thickening of the duct wall but no tumor was identified.

Gross examination of the subsequent specimen of distal cystic duct at the junction with common hepatic duct revealed marked segmental thickening of the wall and narrowing of the lumen. Sections from this area and the common duct at its origin revealed that the thickened wall was caused by a diffuse infiltrate of pale cells with abundant granular cytoplasm, distinct cell borders and uniform small dark nuclei. There was a variable degree of fibrosis interspersed between nests of tumor cells (Figs. 1 and 2). The appearance was that of a typical benign granular cell tumor.

The resected gallbladder had a slightly thickened wall and histologically showed mild chronic cholecystitis.

## COMMENT

The major features of our case and of the six others recorded in the literature are summarized in Table I. [5, 7, 11-13]

Granular cell tumor of common bile duct appears to be prevelant only among people of black origin. All seven cases including our case have been present in blacks and six out of the seven cases occurred in females. The patients ranged in age from 15-46 years, though, the maximum number of cases (3/7) occurred in the third decade.

Two cases were diagnosed at autopsy. One of these patients died of unrelated causes and granular cell tumor was an incidental finding. The other patient died of biliary cirrhosis caused by common bile duct obstruction due to this tumor. The other five cases presented with symptoms and signs of obstructive jaundice and/or cholecystitis. The laboratory studies were consistent with the diagnosis of obstructive jaundice in all the patients who were operated upon except one patient who presented with manifestations of chronic cholecystitis.

The preoperative diagnosis of this tumor is difficult to establish because there are no specific features of this disease. If the patient has had a granular cell tumor previously excised from another site, then, in the presence of obstructive jaundice, this tumor should be considered in the differential diagnosis.

The etiological role of alcohol in this disease is uncertain. In five of the seven cases it was categorically mentioned there was a history of heavy alcohol consumption. This may, however, merely reflect the socioeconomic status of these patients.

The origin of these tumors remains debatable. Abrikosoff,[14, 15] who originally described the lesion in 1926 thought that it arose from muscle cells and therefore called it granular cell myoblastoma. Murray[16] supported this view. Pearse[17] indicated that these tumors derive from fibroblasts. Fust and Custer[18] were the first to suggest that these may be of neural origin. Fisher and Wechsler,[19] after electron microscopy of these tumors, supported this view and suggested their origin from Schwann cells. Mackay, et al[20] did not confirm this view but suggested that although these tumors were of neural origin, they might not come from the Schwann cells. More recently it has been proposed that granular cell tumor may be of diverse histogenetic origin or may arise from primitive mesenchymal cells.[21] For this reason the noncommittal term granular cell tumor is preferred to myoblastoma.

TABLE I

SUMMARY OF CLINICAL AND OPERATIVE FINDINGS IN CASES OF GRANULAR CELL TUMOR OF THE COMMON BILE DUCT

| | Age | Sex | Race | Symptoms | Physical findings | Laboratory findings | Gross findings and procedure |
|---|---|---|---|---|---|---|---|
| Coggins[11] (1952) | 25 | F | B | Anorexia and vague abdominal pain, 1 year; heavy alcohol intake. Weight loss of 9 kg.; jaundice; abdominal distention; lethargy 3 days; coma, 1 hour. | Comatosed; icteric engorged neck veins; pulmonary edema; ascites hepatomegaly | Hemoglobin, 2.4 gm.%; hematocrit, 9%; WBC, 25, 400/cu. mm. | Autopsy, CBD dilated 3.5 × 0.6 cm. mass from ampulla of Vater in CBD. |
| Duncan[12] (1957) | 30 | F | B | Yellow eyes and dark urine; 1 month. Heavy alcohol intake. | Icterus; R.U.Q. tenderness and hepatomegaly; clay colored stools | Bilirubin, 10.4 mg.%; direct, 5.6 mg.%; alkaline phosphatase, 12.8 units. | Rubbery, yellowish grey tumor 2 × 1.5 × 1 cm. at the cystocholedochal junction; dilated hepatic duct; cholecystectomy; excision of mass; choledochoduodenostomy. |
| Whitmore[5] (1969) | 37 | F | B | Pruritus, clay colored stools; chronic alcoholism. | Icterus; enlarged tender liver; mass in L.L.Q. | Bilirubin, 6.1 mg.%; direct, 2.1 mg.%; alkaline phosphatase, 67 SJR units; SGPT, 80. | Hard, gritty, mass in prepancreatic region in the C.B.D.; excision mass; cholecystectomy choledochoduodenostomy. |
| Whitmore[5] (1969) | 61 | F | B | Chronic lung disease *cor-pulmonale;* | Not available | Bilirubin, WNL, 3 occasions. | Died of bronchopneumonia. |

TABLE I *(continued)*

SUMMARY OF CLINICAL AND OPERATIVE FINDINGS IN CASES OF GRANULAR CELL TUMOR OF THE COMMON BILE DUCT

| | Age | Sex | Race | Symptoms | Physical findings | Laboratory findings | Gross findings and procedure |
|---|---|---|---|---|---|---|---|
| Whisnant[7] (1974) | 35 | F | B | Scaling, rash and increasing jaundice; pruritus; anorexia; weight loss, 9 kg.; R.U.Q. crampy pain; clay colored stools; dark urine. | Jaundiced; R.U.Q. tenderness, enlarged liver. | Bilirubin, 20.5 mg.%; alkaline phosphatase, 177 I.U.; SGOT, 110. Stool guaiac positive. UGI, extrinsic pressure on duodenum; transhepatic cholangiogram, dilated duct. | Dilated CBD; solid mass in CBD; cholecystectomy and excision of mass with T-tube drainage; 2nd operation distended CBD; resection of distal CBD; choledochojejunostomy and jejunojejunostomy. |
| Durst[13] (1975) | 15 | M | B | Pruritus; anorexia; intermittent abdominal pain; weight loss; 13.5 kg.; 6 mo. | Icterus; enlarged liver; R.U.Q. tenderness. | Direct bilirubin, 3.2 mg.%; SGPT, 100; alkaline phosphatase, 32 BLB; I.C.G. faintly visualized; gallbladder, normal duct. | 2.5 cm. rubbery mass 2 cm., proximal to ampulla of Vater; cholecystectomy; excision of mass; choledochoduodenostomy. |
| Being reported (1978) | 46 | F | B | Pain R.U.Q. 3 mo.; vomiting 1 day; chronic alcoholism. | Tenderness, R.U.Q.; Murphy's sign positive. | Nonvisualized gallbladder; liver tests, WNL. | Firm mass in CBD about 1 cm. from ampulla of Vater. Cholecystectomy, excision of mass and choledochoduodenostomy. |

CBD—Common bile duct; WNL—Within normal limits; RUQ—Right upper quadrant; LLQ—Left lower quadrant; ICG—Intravenous cholangiogram.

Mackay, et al[20] felt that there may be an infectious origin of these tumors. Lesions at multiple sites in the same patient, occurrence of the same lesions in later life and possible response of these tumors to corticosteroid therapy,[22] lend support to this theory. These authors attempted to isolate spherical particles 30-60 $\mu$ from these lesions but the evidence was not absolutely confirmatory. A form of transplantable granular cell tumor has been described in laboratory mice.[23]

On light microscopy, the tumor is seen to be composed of polygonal cells with scanty stroma. The cytoplasm is eosinophilic and contains multiple coarse granules that stain positively for PAS, and also with Mason's trichrome stain and Sudan black. The small dense nuclei are located centrally.

One of the most characteristic features of these lesions when arising in the tongue, upper respiratory tract and to a lesser degree in skin is the presence of pseudoepitheliomatous hyperplasia of the overlying epithelium. This benign process may occasionally mimic a well differentiated epidermoid carcinoma. Great care must therefore be taken to consider the possibility of an underlying granular cell tumor when atypical squamous proliferation is seen in an unusual clinical setting.

Granular cell tumor is usually a benign tumor in its clinical behavior but cases of locally recurrent tumors[24] and sometimes distant metastases have been described.[25, 26] Histologically, small clusters of tumor cells often appear to be lying detached from the main tumor mass, a feature which should not be interpreted as malignancy.

The patients do well after local excision. All the five cases who had their lesions surgically removed from the common bile duct recovered. Only one patient had to be reoperated for an initial incomplete removal of the tumor. Excision of the tumor with cholecystectomy and choledochoduodenostomy was the procedure performed in four of the five reported cases. It is interesting that four out of five surgeons did the same procedure without knowing the final definite diagnosis. On the basis of the reported cases this procedure seems appropriate for granular cell tumor of the common bile duct.

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## *Clinical Vignette*

# Choledochal Cyst Presenting as Pancreatitis

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A patient with choledochal cyst presenting with recurrent pancreatitis is described. The cyst was suspected on endoscopic retrograde cholangiography (ERCP), then was diagnosed by intravenous cholangiography and abdmoinal angiography. It was confirmed at surgery. The clinical, radiological and surgical features of this disorder are described and the importance of this entity as a possible correctable cause of pancreatitis is stressed.

## INTRODUCTION

Uncommon disorders sometimes present with common symptoms. If the diagnosis can be made correctly, a proper therapeutic approach can be taken. We here report a man with choledochal cyst who presented with recurrent pancreatitis.

## CASE REPORT

A 56-year old Caucasian male was admitted to Allegheny General Hospital for the first time in April, 1968 with complaints of acute abdominal pain, nausea and vomiting of two weeks' duration. A diagnosis of pancreatitis was made. His past history included a laparotomy in 1959 for abdominal pain, at which time a diagnosis of acute pancreatitis was made.

During his first hospital admission the laboratory studies showed: WBC, 12,200/cu. mm.; urine amylase, 910 u./hr. (normal less than 300 Somogyi units), bilirubin total, 1.5 mg.% and direct bilirubin 1.0 mg.%. The patient was treated conservatively with I.V. solutions, nasogastric suction, and anticholinergics and discharged. He was readmitted in March, 1969 with similar symptoms. A diagnosis of alcohol-induced pancreatitis was made. Laboratories studies at this time showed: WBC, 18,100/cu. mm. with shift to the left; serum amylase, 580 u. (normal 50-160 u.); urine amylase, 675 u./hr. The patient was again treated conservatively and discharged. In May, 1971, he was admitted to another hospital with acute pancreatitis and a cholecystectomy was performed. No stones were found in the gallbladder. No abnormal intraabdominal masses were described. No description of pancreatitis was entered on the chart.

On his admission to Allegheny General Hospital in April, 1972, he presented the same symptoms as on the previous admissions. An abdominal examination showed tenderness in the mid abdomen with decreased bowel sounds. Laboratory studies showed: WBC, 12,200/cu. mm.; serum amylase, 166 u.; total bilirubin, 4.8 mg.% and direct bilirubin, 3.5 mg.% This time, as the patient already had a cholecystectomy, a diagnosis of alcohol-induced pancreatitis was made even though

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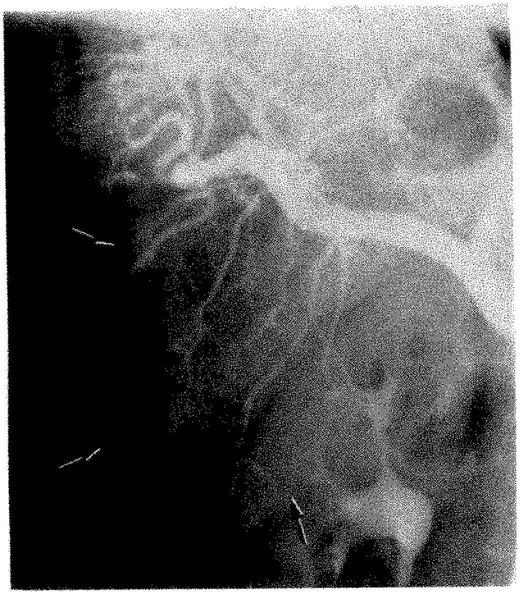

Fig. 1—Choledochal cyst, arterial phase (arrows).

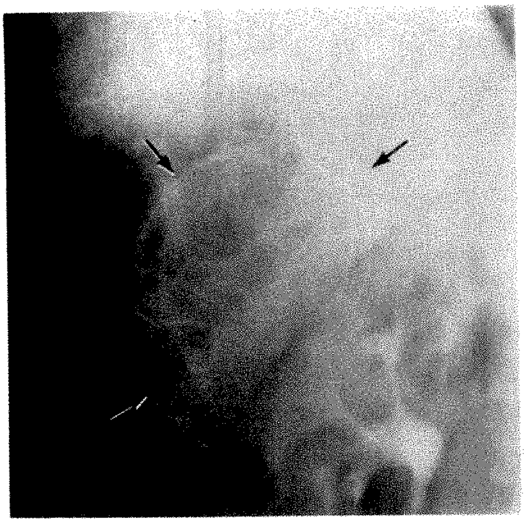

Fig. 2—Choledochal cyst, venous phase (arrows).

the patient denied alcohol ingestion. He was again treated conservatively. During this admission, a liver biopsy showed minimal fatty infiltration with edema of the portal zones. No features of alcoholic hepatitis were present. The patient signed out of the hospital against medical advice. One week later, on 19 April 1972 he was readmitted with abdominal pain, nausea and vomiting. Laboratory studies showed: WBC, 16,400/cu. mm.; urine amylase, 1,056 u./hr.; total bilirubin, 1.2 mg.%; direct bilirubin, 0.17 mg.%. During this admission, he was seen by the Gastroenterology Service. Physical examination revealed some fullness in the right upper quadrant but no definite mass was felt. Work-up included endoscopic retrograde cholangiopancreatogram (ERCP), abdominal arteriography and intravenous cholangiogram.

The ERCP showed a short segment of distal common bile duct communicating with a dilated proximal segment, which was incompletely filled with dye. The procedure was terminated before the remaining portions of the biliary tree were visualized. The dye entered the cystic area and was interpreted as a possible extravasation. A displacement of the pancreatic duct superiorly was interpreted as secondary to an extrinsic mass. The pancreatic duct did not show any changes consistent with chronic pancreatitis. The common bile duct was not fully visualized.

An intravenous cholangiogram revealed a vague accumulation of dye in the right upper quadrant suggestive of a choledochal cyst. The dye collection was even more apparent on a delayed film four hours after the I.V.C. was performed.

Abdominal arteriogram showed a cystic lesion, 10 cm. in diameter, in the right upper quadrant deriving its blood supply from the right hepatic artery (Figs. 1 and 2). Upper gastrointestinal films showed a large mass posterior to the duodenum enlarging the loop.

Exploration on 1 May 1972 revealed a Type I choledochal cyst approximately 12 cm. in diameter. Choledochocystojejunostomy and jejunostomy were performed.

The postoperative course was uneventful except for a transient right hemiparesis which cleared rapidly. Two weeks after surgery, the patient was discharged in satisfactory condition. Despite the fact that the patient continued to use alcohol after surgery, he remained totally asymptomatic until a metastic melanoma caused his death four years later. No autopsy could be obtained.

## COMMENT

This case shows an unusual presentation of choledochal cyst as recurrent pancreatitis in a man, 50 years old. In fact, the symptoms started at the age of 35. Initially the symptoms were attributed to alcohol ingestion, though the symptoms continued after he discontinued drinking. The symptoms were then blamed on the gallbladder disease but they persisted even after a cholecystectomy was performed in 1971. Interestingly enough although the patient was operated upon twice, choledochal cyst was not mentioned in either of the two surgical reports. Considering that the etiology of choledochal cyst is congenital, it should have been discovered at the time of surgery, unless our patient had a hypoplastic common bile duct and after the cholecystectomy thte duct became dilated due to removal of the gallbladder that was acting as a reservoir.[1-3] The diagnosis of choledochal cyst was suspected on I.V.C., ERCP and abdominal angiogram. It was finally confirmed at laparotomy.

The usual symptoms of choledochal cyst are a triad of pain, jaundice, and a palpable right upper quadrant mass.[4, 5] Our patient presented with recurrent abdominal pain, jaundice and right upper quadrant fullness, but not a discrete mass.

The complications of choledochal cyst are largely due to biliary obstruction.[4-6] Complications include: stone formation, suppurative cholangitis, biliary cirrhosis, hepatic abscess and thrombosis of the portal vein.

Choledochal cyst presenting as pancreatitis has been described only rarely. There have been only four cases reported where choledochal cyst presented as pancreatitis.[7-10] Three of the four cases were adults and a fourth was a four-year old girl. Among the three adults, one patient had a choledochocele, a variant of choledochal cyst.

The etiology of pancreatitis in choledochal cyst is not clear. Various speculations have been made. One theory is of pancreatic duct obstruction or bile stasis within the pancreatic duct and activation of proelastin to elastin. It is also proposed that intrapancreatic activation of phopholipase A may play a role in the etiology of pancreatic necrosis.[11]

The surgery of choice is choledochocystojejunostomy.[1, 12] Our patient continued to remain asymptomatic four years after surgery until his death due to metastic melanoma.

There can be several questions raised regarding the etiology of pancreatitis in our patient. Was the pancreatitis caused by choledochal cyst or alcohol? As mentioned above, this patient continued to have symptoms of abdominal pain with increased amylase levels in spite of his unequivocal denial of alcohol ingestion. His pancreatogram was normal on ERCP. Unless the patient gave us an inaccurate history, why would he be symptom-free after a choledochocystojejunostomy? Why were the surgeons unable to appreciate or describe a big 12 cm. choledochal cyst? That is a question we cannot answer. The only alternative explanation can be that our patient probably had a hypoplastic common bile duct. Hypoplastic common bile duct in absence of the gallbladder and normal or increased distal sphincteric pressure, results in a choledochal cyst.[1-3] This theory, although it sounds good, has not been very well accepted and proven.

## ACKNOWLEDGMENTS

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## *Clinical Vignette*

# A Case of Benign Main Pancreatic Duct Obstruc
# Mimicking Pancreatic Carcinoma

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Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated obstruction of the main pancreatic duct at the body of the pancreas. Pancreatic scintigraphy, ultrasonography and celiac angiography suggested a space-occupying lesion in the body of the pancreas. A tentative diagnosis of carcinoma of the pancreas was made and resection of the body and tail of the pancreas was carried out. The resected specimen, however, failed to demonstrate any malignant cells on histopathologic examination. Instead, section revealed fatty replacement of the gland with obliteration of the pancreatic duct in the distal half of the resected pancreas.

Between 1970 and 1972, a number of studies of the normal and abnormal pancreatogram, obtained by retrograde injection of the duct during ERCP, described the characteristics of changes produced by malignancy and inflammation.[1-3] Complete ductal obstruction was interpreted as indicating cancer by most, although doubt was expressed by some.[4-6] The
report illustrates a rare cas
obstruction of the duct of \
flammatory disease with fatt
of the parenchyma distal to t

### REPORT OF CAS

A 53-year old woman d
a thorough check-up of th
gastrointestinal tract, becau
cently experienced transient
Fifteen years ago, she had al
rent pain in the left lumbar
for a year and half. The th
received and the diagnosis
time were unknown.

Physical examination ar
laboratory tests were of no va
normal limits except for slig
serum amylase, i.e. 226 U. (n
No abnormality was seen i
meal study of the upper
tract. Pancreas scintigraphy
lignancy of the body and ta
radioisotope uptake in this
gland was poor. The ERCP
ducts. The biliary tract was
to the intrahepatic bile duc
normality. The main pa
showed an obstruction at t
irregular dilatations of the

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A case of fatty replacement of the body and tail of the pancreas is reported.

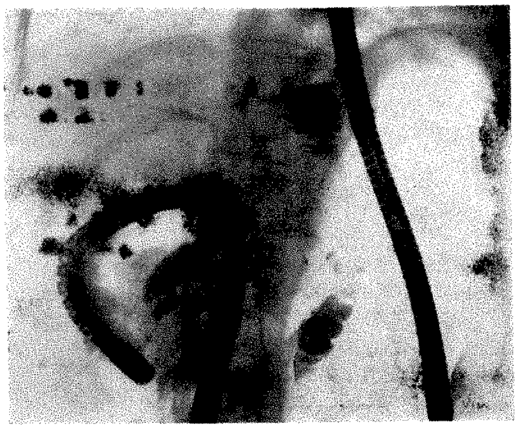

Fig. 1—ERCP in an almost supine position. The main pancreatic duct is completely obstructed, with irregular cystic dilatations of the branches adjacent to the obstructed part at the distal body. The common bile duct is slightly dilated.

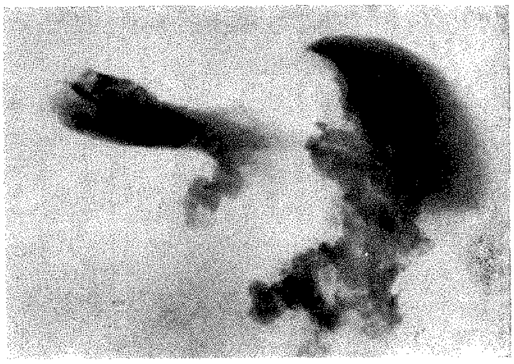

Fig. 2—Preparation of the resected specimen. Complete replacement by fatty tissue at the site of the tail of the pancreas. Acinar cells can be seen at the duodenal site (Hematoxylin and eosin, original magnification x10).

the obstructed part (Fig. 1). Cytology of the pure pancreatic juice was negative for cancer cells. Celiac angiogram showed numerous branches arising from the dorsal pancreatic artery; a few of these branches showed slight displacement. Ultrasonography revealed irregular inner echoes within the pancreas, although the size of the pancreas was normal.

Because these findings suggested a small pancreatic body and/or tail carcinoma, resection of the body and tail of the pancreas was carried out.

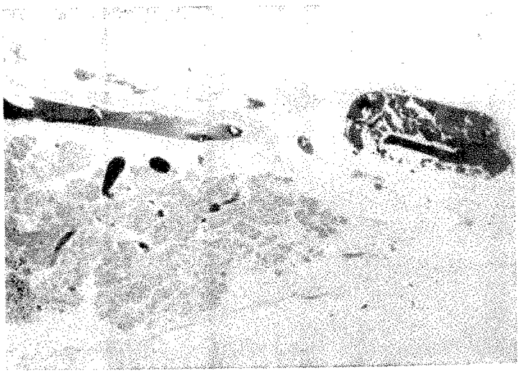

Fig. 3—Pancreatic ductgram of resected specimen, used 50% Urografin, shows almost the same findings such as ERCP.

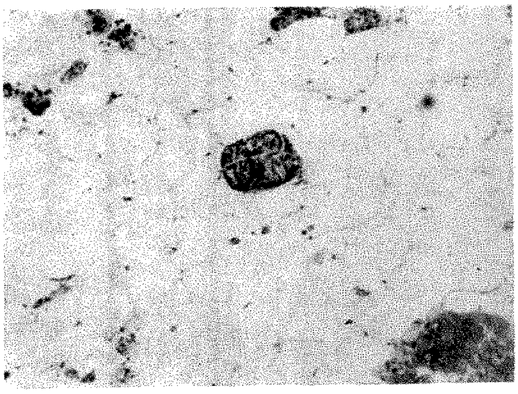

Fig. 4—Islet cells in the tail of the pancreas. This proves that this site in the pancreas is replaced by fatty tissue (Hematoxylin and eosin, original magnification x100).

Grossly resected specimen did not show any recognizable pancreatic tissue in the distal half of the pancreas which felt soft and fatty. (Fig. 2). A pancreatic ductogram done on the resected specimen, using 50% Urografin, confirmed the findings of ERCP (Fig. 3). A few islet cells, however, were found in the fatty distal pancreas (Fig. 4).

The postoperative course of this patient was uneventful and she was discharged without any complication or sequels.

## COMMENT

When the obstruction of the main pancreatic duct is visualized on ERCP following injection of sufficient contrast medium, it is customary but erroneous to consider that the cause of obstruction is pancreatic carcinoma. There are benign disorders which produce an obstruction of the main pancreatic duct.[6, 7]

This case is probably the result of gradual obstruction of the main pancreatic duct due to chronic pancreatitis as suggested by the past history of pain in the left lumbar region 15 year ago. We believe that gradually increasing inflammatory stricture was accompanied by progressive fatty replacement of parenchyma. More rapid ductal occlusion as seen in carcinoma results in inflammatory fibrosis.

One might ask if surgery and pancreatic resection could be avoided in such cases. It is clear that anatomic configuration of the duct (ERCP) can be misleading. Cytology, especially with an occluded duct, appears to yield a low positive percentage of cancer cells in carcinoma of the body and tail.[8, 9] Scintigraphy and sonography can only define space-occupying lesions. Perhaps, in cases of doubt, sonographic guided percutaneous needle biopsy may yield the most significant data.

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***Clinical Vignette***

# Ileovesical Fistula

## FAILURE OF T.P.N. ROLE OF ORAL $^{14}C$ PEG (POLYETHYLENE GLYCOL) AND CHARCOAL IN DIAGNOSIS

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A patient with regional enteritis presenting with symptoms of fecaluria and pneumaturia is presented. Most of the established technics such as upper gastrointestinal series, cystography, cystoscopy and colonoscopy failed to demonstrate the fistula in this patient. $^{14}C$ PEG as a nonabsorbable marker was given by mouth and a seven-fold increase in the counts at the fourth hour of urine collection confirmed the presence of an ileovesical fistula. This increase in counts was not seen when $^{14}C$ PEG test was repeated after closure of this fistula surgically and was also not seen in a similar disease control patient and a healthy normal volunteer.

Total parenteral nutrition with intralipids, Freamine II and glucose given in a peripheral vein for 45 days failed to close this fistula.

Fecaluria and pneumaturia are very rare symptoms caused by ileovesical or colovesical fistula. The earliest description of the above mentioned symptoms was by Wagner[1] in 1685 in a case of colovesical fistula. The number of cases of colovesical fistula far exceeds the cases of ileovesical fistula. The most common cause of colovesical fistula is diverticulitis[2-4] and the other common causes are carcinoma in the sigmoid colon, rectum, female genitalia and urinary bladder.[5] One has also to consider some uncommon causes such as radiation treatment. Crohn's disease of the colon, ulcerative colitis, trauma; fungal and parasitic diseases of the colon should also be considered.[4, 6, 7]

Ileovesical fistula is a very rare entity[8-10] and is almost entirely confined to regional enteritis. Ileovesical fistula is rare according to Greenstein, Kark and Dreiling[11] who, from 1944-1973, found only four cases of ileovesical fistula out of 160 well proven cases of regional enteritis.

There have been great strides made in the treatment and diagnosis of intestinal fistula in general but very little literature is available on the diagnosis and treatment of ileovesical fistula. The diagnosis of ileovesical fistula is suggested by the dramatic symptoms of pneumaturia and fecaluria and sometimes can be confirmed by giving charcoal or mineral oil by mouth and noting

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From the Department of Gastroenterology, Monroe Community Hospital and the Department of Pharmacology, University of Rochester School of Medicine and Dentistry.

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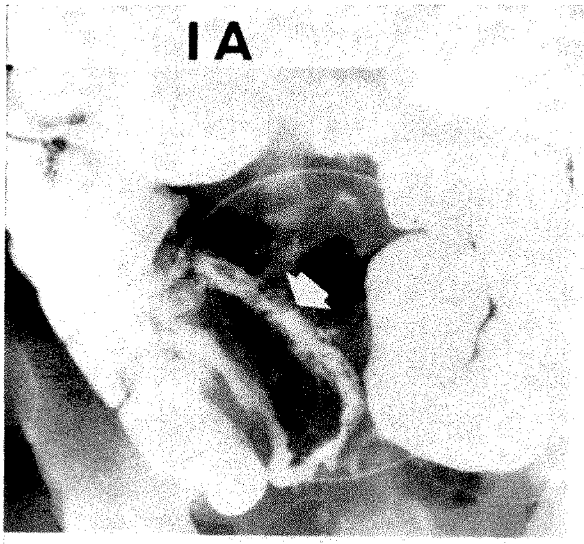

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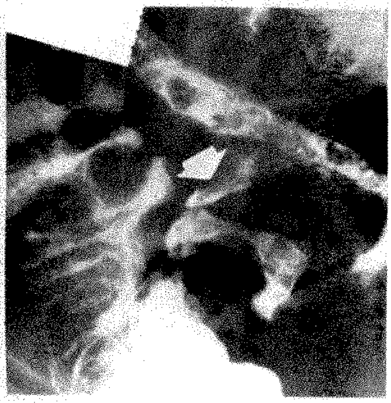

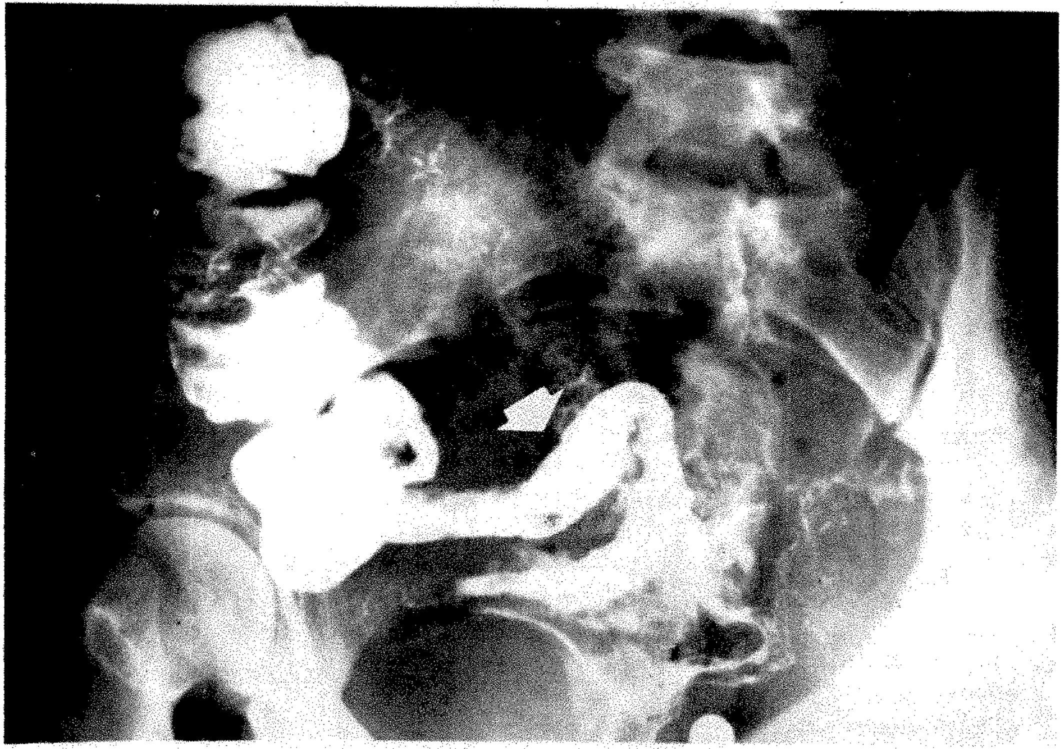

1C

Fig. 1A—Patient K. R.—Upper gastrointestinal barium follow through studies showing regional enteritis (arrow) in the terminal ileum. No fistula was seen.

Fig. 1B—Patient K. R.—Second barium enema done after 45 days of TPN showing fistula arising from terminal diseased segment (arrow). The first barium enema done was normal.

Fig. 1C—Patient A. W.—24-year old white female showing almost similar regional enteritis of terminal ileum (arrow).

these substances in the urine. Other methods used are cystoscopy, cystography, barium follow-through, barium enema and radioactive colloided $Au^{198}$ studies.[8-10, 12-14] In spite of all these technics, the localization of the fistula may remain in doubt.

The availability of total parenteral nutrition has made a significant difference in the management of the cases of intestinal fistulas in general but very little information was available about the role of TPN in ileovesical fistulas.

In our case of ileovesical fistula most of the recognized methods of confirming the diagnosis of ileovesical fistula failed as did TPN in closing the fistula. A novel method of diagnosing the fistula by oral $^{14}C$ PEG and finding it in urine, is described. The validity of the technic was confirmed in another patient with similar disease in the same location, a healthy control and the patient as his own control after surgery of this fistula.

## Materials and Methods

K. R., a 22-year old (#80-69-82) black single male was seen by us on 25 February 1976 with a history of pain for the last two months in the right groin, only on micturition and defecation. He also had a history of occasional loose bowel movements for the same period of time. In addition, he passed black stools only once during the last two months. The patient lost 9 kg. and looked pale. He complained of dull aching pain in the abdomen especially after meals, lasting for 1-2 hours. He had fever without chills which was episodic with a precipitous drop for the last 3-4 weeks. The patient smoked about 15 cigarettes a day.

Physical examination was totally negative. All the investigations, including barium enema (no reflux into the ileum) and an upper gastrointestinal series, were negative. The only significant finding was the presence of sickle cell trait.

On 11 March 1976 he presented with pain in the right testicle of short duration. Nothing else was detected and he was sent home with reassurance.

On 20 March 1976 he came to emergency with dysuria, fecaluria and pneumaturia. Urine showed a heavy sediment on centrifugation. Physical examination showed tenderness in both groins.

He was admitted with the provisional diagnosis of enterovesical fistula due to regional enteritis.

Upper gastrointestinal series, with a follow-through to visualize the terminal ileum, was done which demonstrated the involvement of the terminal ileum (Fig. 1A). No fistula was demonstrated.

Tests to localize the fistula without any success were IVP; cystography and cystoscopy; colonoscopy; $^{99m}Tc$ DPTA scan. The radioactive material is injected intravenously and is excreted into the urinary bladder. The films taken over the pelvis and bladder pre- and postmicturition failed to reveal any abnormally localized activity and no fistula was demonstrated.

The patient was started 29 March 1976 on total parenteral nutrition by peripheral vein using 83% intralipid calories and 17% glucose and Freamine II calories. The patient gradually stopped having fecaluria and pneumaturia. He became asymptomatic within three to four days of starting the therapy. He was started on Azulfidine 2 tablets q.i.d. on 1 April 1976. The patient was not given steroids due to fear of infection.

$^{14}C$ PEG test was done on 21 April 1976. The patient was kept NPO after midnight. He was given 5 $\mu C$ of $^{14}C$ dissolved in 200 ml. of water by mouth and was asked

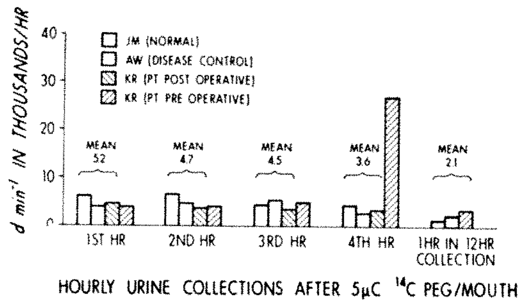

Fig. 2—A bar diagram showing the hourly collection of urine on the abscissa after giving 5 $\mu$C of $^{14}$C PEG by mouth and counts in thousands/1 hr. collection on ordinate. Note that only the K. R. with ileovesical fistula shows seven-fold increase in counts in the fourth hour specimen preoperatively. The counts come down to controls after surgery in this patient. The counts never rise to more than their base value in another similar disease control patient (A. W.) and a healthy normal volunteer.

to empty his bladder. This control urine sample was saved. Urine was collected every hour for four to six hours and all specimens were saved. After the completion of six hourly collections, a 12-hour sample was collected in a sample bottle. All the specimens—one control, six hourly and one 12-hour sample were counted in a Packard Tri-carb scintillation spectrometer. Counting efficiency for $^{14}$C PEG was 85-88%. All values of radioactivity were corrected for quenching and background.

The charcoal given by mouth was detected in the fourth hour sample of urine on 23 April 1976. On 5 May, since the fistula was not closing, the hyperalimentation was stopped and a decision was made to operate.

Before surgery the barium enema was repeated which revealed the presence of an ileovesical fistula (Fig. 1B).

On 7 May the patient was operated upon and a fistula between the small bowel and posterior aspect of the urinary bladder was detected and excised. The cecum was transected just above the ileocecal valve. The terminal 30 cm. of small bowel was resected and an ileoascending colon anastomosis was performed. The patient recovered uneventfully after the operation and is doing well without any medications.

The $^{14}$C PEG test was repeated eight days after surgery.

A 24-year old white female (A. W.) suffering from a similar involvement of the terminal ileum (Fig. 1C) with Crohn's disease without any fistula was also given the $^{14}$C PEG test after proper explanation and permission.

A $^{14}$C PEG test was also done on one of the authors (J. M.) as a normal control.

## RESULTS

Barium enema, upper gastrointestinal series with follow-through, cystography, cystoscopy and $^{99m}$Tc DPTA scan were all unsuccessful in demonstrating the fistula.

The results of the $^{14}$C PEG are illustrated in Figure 2 which shows a seven-fold increase in the counts at four hours in the preoperative urine sample of the patient (K. R.). The total 18-hour sample of urine shows only a minor absorption of $^{14}$C PEG from the gastrointestinal tract. It is also possible that the label $^{14}$C becomes detached from PEG during its transit through the gastrointestinal tract.

The $^{14}$C PEG test results reached normal values after surgery of the fistula and here the patient served as his control.

Another patient (A. W.) with almost similar involvement of the terminal ileum did not show any unusual elevation of counts up to six hours. This disease control was necessary to show that abnormal mucosa does not absorb the PEG spuriously.

The normal healthy control, J.M., revealed similar $^{14}$C PEG counts as did K. R.

(postoperatively) or A. W. (similar disease control).

It is interesting to note that charcoal also appeared in the fourth hour as did $^{14}C$ PEG.

After starting the patient on TPN his abdominal symptoms of cramps and diarrhea disappeared. He gained weight and was in much better condition for surgery. Even after a trial of 45 days the fistula did not close.

## COMMENT

One of the hallmarks of regional enteritis is the development of internal fistulas, external fistulas or a fistulous tract. The incidence reported in one series was as high as 39%.[11] Ileovesical fistula is almost exclusively confined to regional enteritis and fortunately this complication is very rare. Most of these ileovesical fistulas developed after many years of disease activity[11] but in K. R. it was an acute occurrence after a relatively short and mild disease. The patient started with symptoms of dysuria and only later on did diagnostic features of pneumaturia and fecaluria become evident.

There is a plethora of articles stressing the use of total parenteral nutrition in the management of gastrointestinal fistulas.[15] McPhayden and Dudrick[16] reported 62 patients treated with hyperalimentation obtaining a spontaneous fistula closure in 70.5%, with an over all mortality reduced from 40-65% to 6.45%. Himal[17] reported 74 cases treated with TPN with a spontaneous closure rate of 56%. Besides spontaneous closure, hyperalimentation improved the patients nutritionally so that they could withstand surgical closure. Edmund, et al[18] reviewed 157 patients treated at Massachusetts General Hospital and noted that 61% of all malnourished patients with fistulas died. Chapman, et al[19] noted that after optimal nourishment 89% of the patients with fistulas healed while only 37% who were suboptimally nourished, healed. Total parenteral nutrition helps spontaneous closure of the fistula, restores nutrition, induces remission[20, 21] and prepares a debilitated patient for surgery.[22] Most of the cases of ileovesical fistula in the literature were finally operated upon. Considering the nonavailability of TPN before and encouraged by the excellent results in other fistulas, we tried TPN in our patient. The patient improved nutritionally and symptomatically, but failed to close the fistula spontaneously even after 45 days of TPN. The side benefit of TPN is that the patient may be in remission of disease and good nutritional status for surgical closure.

The detection and localization of enterovesical fistula is very important. The symptoms of fecaluria and pneumaturia are almost diagnostic but one has to be absolutely sure because surgery in a patient with regional enteritis should not be undertaken without solid proof. In spite of all the technics mentioned in the introduction, i.e. barium enema, upper gastrointestinal studies with follow-through, cystography, cystoscopy, sigmoidoscopy, colonoscopy, the diagnosis of fistula could not be confirmed. Bernard[12] has suggested the collection of urine before and after barium enema examination and then roentgenography of the centrifuged samples. Since the barium enema in our patient did not show a fistula, I doubt if this method would have worked. After exhausting all the possibilities, renal excretion scan isotope $^{99m}Tc$ DPTA was used because it is supposed to excrete into the urinary bladder. Even this method was not successful. Finally, we tried $^{14}C$ PEG which is a very large molecule and is not absorbed by the gastrointestinal tract. The seven-fold increase of counts in the fourth hour urine sample preoperatively in the patient left no doubt about the fistula. The very fact that some radioactivity was seen in the urine in a normal volunteer, a diseased control and the patient after surgery only points to two possibilities. It is possible that a minor amount of PEG is absorbed or the label of $^{14}$C is split off from PEG during its transit in the gastrointestinal tract and absorbed to be excreted finally by the kidneys. At any rate, the radioactivity absorbed is too miniscule to be of any harm to the patient. It is interesting to note that after PEG, the charcoal also appeared in the fourth hour sample of urine. After confirming the presence of the fistula by $^{14}$C PEG the patient had a repeat barium enema after giving glucagon and this time it was possible to show the fistula. It is entirely possible that glucagon might have relaxed the bowel, caused more reflux of barium or the fistula might have increased in size.

In the end we must admit that although even a single case presented above in such a dramatic fashion with adequate controls is important, more cases are needed to establish this technic on a sound footing. The rarity of this complication may prompt other centers to try this method. This case also points to the limited value of total parenteral nutrition in the closure of ileovesical fistula.

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***Clinical Vignette***

# Partial Duodenal Obstruction in Presence of Complete Rotation of the Colon

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Two children were admitted with partial obstruction of the duodenum due to its incomplete rotation and fixation. The colon in both cases was rotated normally. Our experience with these children, along with embryological evidence to understand the above entity, is presented.

## INTRODUCTION

Partial or complete duodenal obstruction due to malrotation is a known entity among infants and children. Recently two infants were admitted to the Pediatric Surgery Unit of Nehru Hospital, Chandigarh, with partial obstruction of the duodenum where the colon was normally rotated but the incomplete rotation and fixation of the duodenum resulted in obstruction. In this report, we present these two cases and discuss the embryology in detail in order to understand the basic pathology.

## CASE REPORTS

*Case 1:*—A two year old girl was admitted because of recurrent bile stained vomitings since early infancy. Repeated local hospitalizations and plain roentgenograms resulted in no specific diagnosis or improvement. The child at admission was thin and mildly dehydrated. Physical examination was not remarkable. After correction of her electrolytes and fluid deficit, a roentgenogram, using barium, revealed dilatation of the duodenum with narrowing in the third portion suggesting intrinsic stenosis (Fig. 1). The barium enema showed a normally rotated colon. At operation the cecum was mobile and the colon was normally rotated. The right colon was rotated to the left side of the peritoneal cavity which revealed the first and second parts of the duodenum to be dilated. Distal to the dilatation, the duodenojejunal loop rested beneath the superior mesenteric artery where it was bounded by adhesions. The loop was freed of adhesions and rotated to the right. A Ryle's tube was passed and extended through the second part of the duodenum. Saline was injected to exclude any intrinsic obstruction. The postoperative period was uneventful. There was no further vomiting and the child, one and half years postoperative has gained weight.

*Case 2:*—A four and a half-year old male was admitted because of repeated episodes of crampy pain and nonprojectile vomitings, after meals since early infancy. The vomitus used to be foul smelling and no bile was noted. The child never gained weight and was in poor health. Roentgenogram with thin barium revealed dilatation of the first and second upper portion of the duodenum with narrowing of the third portion (Fig. 2). Surgery revealed the colon

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From the Department of Pediatric Surgery, Postgraduate Institute of Medical Education and Research.

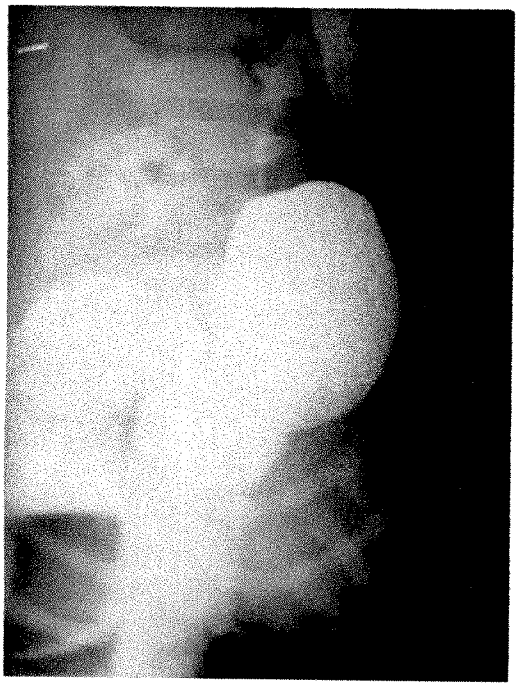

Fig. 1—Barium meal showing dilatation of the first and second portions of the duodenum with sudden stoppage at the third portion.

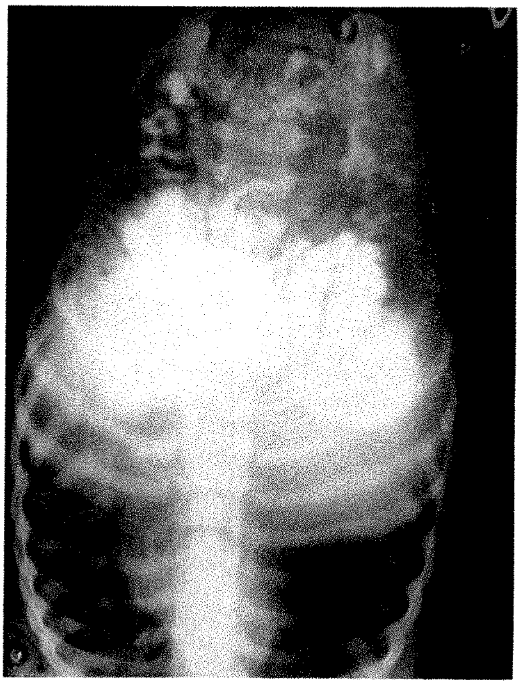

Fig. 2—Barium meal showing the second portion of the duodenum with some dye in the small bowel obstruction at the third portion seen at screening.

to be normally rotated. The right colon was rotated to the left to show the duodenojejunum ending at the superior mesenteric artery and slightly anterior to the artery. The loop was fixed by adhesions. It was rotated to the right and the obstruction was released. The intrinsic duodenal obstruction was excluded as in the first case. The child was completely relieved and now one year after operation is free of symptoms and has gained weight.

## EMBRYOLOGY

The rotation of the intestines has been well documented in the literature.[1-4]

At one month of fetal life, the intestinal tract represents almost a straight tube with a slight anterior bulge in the central portion. The superior mesenteric artery comes forward from the posterior wall to the center of the bulge. As the intestine forms within an extension of the abdomen into the cord, the rapid changes occur. The stomach remains anterior and above the superior mesenteric artery. Later the duodenum begins to rotate counter clockwise, curving 90° downwards and to the right of the artery, where the rest of the mid gut from jejunum up to transverse colon extends into the umbilical cord. The rotation of the duodenojejunum continues during the extracoelomic phase of development of the intestines. In about the eighth week, when the embryo is about 23 mm. the third portion of the duodenum comes to rest beneath the superior mesenteric artery (a rotation of 180° occurs). At the 10th week, the small intestine returns to the abdomen and at this stage pushes the fourth part of the duodenum and proximal jejunum to the left of the superior mesenteric artery thus completing the rotation of the duodenojejunum 270° counterclockwise. The cecum and colon also finally complete the 270° counterclockwise rotation at the cecocolic loop. The attachment of the small and large intestines to the posterior wall follows the rotation of these loops.

In malrotation the duodenum may be obstructed by bands crossing the duodenum from the incompletely rotated cecum to the inferior surface of the liver or to the posterior portion of the peritoneum. If, however, the duodenojejunal loop fails to complete its normal rotation and becomes fixed by adhesions in the region of the superior mesenteric artery obstruction may occur. This abnormal fixation may cause angulation and kinking. As mentioned previously, the duodenojejunum rotates 180° to the region of the superior mesenteric artery before withdrawing of intestines. Final rotation of the duodenojejunum seems to be related to the pressure of the intestines, with drawing from the cord. The duodenojejunum may become fixed prior to its final rotation, resulting in an incompletely rotated duodenojejunum in the presence of an either incompletely or completely rotated colon. The severity of the obstruction depends on the hyper- and hypofixation of the duodenum.[5]

## COMMENT

The two cases are typical of partial duodenal obstruction resulting from incomplete rotation and fixation of the duodenojejunum loop. The diagnosis is mainly dependent on roentgenography to visualize the contrast material passing through the duodenum and to localize the obstruction at a definite anatomical point. In both cases the colon was normally rotated and the cecum was mobile. The colon was rotated to the left and the third and fourth part of the duodenum and duodenojejunum loop were seen fixed due to adhesions. These bands were dissected as done in Ladd's procedure[6] and rotation of the duodenojejunum loop was done towards the left side up to the extent that the mesentery was raised from the posterior abdominal wall to prevent recurrent obstruction. In both cases we ruled out internal obstruction and the results were excellent following surgery.

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# State of the Art*

## UPDATE: BIG DUCT, LITTLE DUCT OR TOXIC METABOLIC PATHOGENESIS OF PANCREATITIS

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Concepts of pathogenesis of pancreatic inflammation have undergone marked evolution since the classical hypotheses formulated by Opie,[1] Archibald,[2] Rich and Duff.[3] These hypotheses, permutations of sphincter dysfunction, anatomic common channel and biliary regurgitation presented discrepancies with experimental and clinical data which conceivably could be resolved for biliary tract pancreatitis but not alcoholic pancreatic inflammation. It was difficult to explain: 1. the occurrence of pancreatitis in patients without a common channel; 2. the failure of pancreatic inflammation to develop in patients with demonstrated common channels and 3. the feasibility of biliary regurgitation against a pressure gradient (Table I).

These discordances resulted in a reinterpretation of the data which retained the mechanistic principles but implicated pancreatic duct obstruction or pancreatic ductal hypertension rather than biliary reflux as the factor inciting pancreatic inflammation.

The "mechanistic" pathogenesis was interpreted by us as the "big duct hypothesis". According to this hypothesis the effect of alcohol was local in the stomach and duodenum.[4] In the stomach alcohol induced the secretion of HCl which, on entering the duodenum, released secretin. In the duodenum, alcohol caused inflammation and spasm of the sphincter of Oddi. The secretin-induced pancreatic flow was thus secreted against pancreatic duct obstruction, the pathogenic sequence being: 1. stimulation of the gland against obstruction; 2. increased pancreatic ductal pressures; 3. rupture of the finer ductal radicals; 4. releasing activated pancreatic ferments into the interstitial tissues, producing; 5. chemical inflammation and autodigestion. This pathogenetic sequence seemed applicable as well to the pancreatitis associated with duodenal obstruction.

Sarles[5] interpreted the mechanistic factor somewhat differently and evolved the "small duct" hypothesis. This pathogenesis placed the site of pancreatic duct obstruction in the ductules. The cause of obstruction was hypothesized to be due to the precipitation of protein plugs which were noted by the Sarles group in histologic sections of chronic pancreatitis.

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TABLE I

Pressure Relationships in the Pancreatic and Biliary Tracts in Man

| | mm. $H_2O$ |
|---|---|
| Pancreatic secretory pressure | 300-500 |
| Hepatic secretory pressure | 200-300 |
| Gallbladder contraction pressure | 170 |
| Sphincter resistance pressure | 250 |
| Common duct—intersecretory pressure | 50 |
| Common duct—postcholecystectomy | 190 |

The "big duct" hypothesis failed to explain three clinical observations: 1. the latent period of alcoholic pancreatitis—at least 3-4 years of heavy drinking precede alcoholic pancreatitis; 2. the failure of initial or incidental alcoholic excesses to precipitate acute pancreatitis; 3. pancreatography performed during acute pancreatitis which does not show isolated ductular rupture but rather diffuse loss of ductular integrity with permeation of the interstitial tissue by the introduced contrast medium.

Spiro[6] neatly summed up the difficulty by stating the opinion that the initial attack of acute alcoholic pancreatitis represented, in fact, an acute exacerbation of chronic pancreatitis.

Elucidation of these clinical discrepancies resulted from physiologic experiments which showed that: 1. the first response of the pancreas to minimal injury is ductular reduplication by hypertrophy and hyperplasia in an attempt to regenerate the pancreas.[7-9] 2. this regeneration was accompanied by hypersecretion of fluid, electrolyte and protein; 3. hypersecretion could be detected by pancreatic secretion studies in a number of situations in which clinical pancreatitis was not observed; 4. hypersecretion could be detected in patients with manifest chronic pancreatitis.[10]

The Sarles group seized upon hypersecretion as the cause of protein plug precipitation. Tiscornia[11, 12] had shown, in dogs made alcoholic, that alcohol initially depressed pancreatic secretion. Later there was hypersecretion due to increased liberation of CCK-PZ, increased vagal activity and increased sensitivity of the ascinar cell to CCK-PZ. Extrapolated to man, these data are consistent with the "small duct" hypothesis.

To Bordalo and me, the demonstration of hypersecretion in alcoholic cirrhotic patients and in chronic alcoholics without manifest pancreatitis suggested the possibility that metabolic disruptions at the cellular level might result from alcoholism and that these might be the basis for the observed hypersecretion. Routine microscopic and electronmicroscopic sections of human pancreases obtained by biopsy in alcoholic patients with and without manifest clinical pancreatitis have disclosed the following lesions within the acinar cell primarily and to a lesser degree the adjacent ductular cells: [13, 14] 1. deposition of intracellar fat droplets; 2. hypertrophy and dilation of the endosplasmic reticulum; 3. distortion and enlargement of the mitochondria.

I (D. A. D.) believe these charges, so reminiscent of the toxic metabolic effect of alcohol on the liver, are the initial lesion inflicted by alcohol on the pancreas.

## Summary

In summary, we should like to formulate a new hypothesis of pathophysiology of alcoholic pancreatitis and to construct from the evidence presented a new pathogenetic mechanism for alcoholic pancreatitis supplanting the classical mechanistic thesis. A strong parallelism exists between the pancreas and the liver. In the latter, it is clear that prolonged ingestion of excessive quantities of ethanol induces endoplasmic

reticular hyperplasia, causes specific and nonspecific enzyme induction and is associated with electronmicroscopic aberrations of the mitochondria. The sum total alterations in metabolic pathways results almost invariably in the accumulation of fat in the liver as a result of the well documented diversions of oxidative metabolism. In the pancreas of alcoholics, the metabolic alterations induced by ethanol have not been elucidated to date but the histologic effects of injury are documented as endoplasmic reticular hyperplasia, mitochondrial distortion and fat deposition, changes identical to those observed in the liver. The physiologic effects of these alterations are increased secretions of proteinaceous material and increased flows in response to secretin presumed to result from ductular reduplication induced by injury. In the liver, the metabolic alterations proceed in some alcoholics to a point at which there is gross cellular damage as indicated by alcoholic hepatitis from which continued alcoholism inexorably progresses to a cycle of liver cell necrosis, repair and fibrosis, all characterizing cirrhosis. In the pancreas, this would correspond to the development of an attack of clinically manifest acute pancreatitis, again induced in a group of apparently susceptible alcoholics by factors incompletely understood. Here too, there commences a cycle of parenchymal necrosis, repair and fibrosis with calcification resulting in clinically manifest chronic alcoholic pancreatitis and its convential pathology. Associated with these developing pathologies, the secretory response of the gland to secretin shifts from the hypersecretory state through normal flows and, eventually, in the markedly diseased gland, to decreased secretion. Concomitant with these changes in flow is a gradual deterioration in the ability to secrete bicarbonate. Under certain circumstances this pathologic sequence apparently may cease and there then results a regeneration of parencyma and a restoration of function.

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# The Pediatric Corner

## PRIMARY PULMONARY HYPERTENSION PRESENTING AS PORTAL HYPERTENSION

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A two and a half-year old child is described who presented with signs of portal hypertension (hematemesis, hepatosplenomegaly, ascites). Her subsequent work-up revealed that the "pressure-head" originated within the pulmonary arterial bed. Indeed, severe changes of primary pulmonary hypertension were found at autopsy. What is unique about this case is the absence of cardiopulmonary symptoms prior to the development of suprahepatic portal hypertension. In addition, the pulmonary disease developed in the absence of underlying chronic hepatic disease or extrahepatic portal vein thrombosis which, reportedly, can lead to pulmonary hypertension.

The sudden presentation of suprahepatic portal hypertension, a rare condition in the pediatric age group, is most likely to be associated with hepatic vein occlusion due to sickle cell anemia, allergic vasculitis, polycythemia, leukemia, inflammatory bowel disease and veno-occlusive disease, often toxin or drug-induced. Other unusual causes of suprahepatic portal hypertension include tumor obliterating the hepatic vein lumen, hepatic vein and supradiaphragmatic inferior vena cava webs or diaphragms, constrictive pericarditis and congestive heart failure when an etiology has indeed been found.[1-4] The clinical entity presents with expanding abdominal girth due to hepatomegaly and ascites. In addition, splenomegaly, collateral portal circulation, abdominal pain and occasionally jaundice can be expected findings. Increased postsinusoidal pressure is transmitted retrograde to the portal vein, giving rise to characteristic hepatic histopathology and the progression of portal hypertension. While the source of the obstructive lesion resulting in suprahepatic portal hypertension has been described from the level of the right heart or pericardium,[4] this case is most unusual in that despite severe pulmonary arterial hypertension she presented with clinical signs of portal hypertension. The vast majority of children with primary pulmonary hypertension succumb suddenly before age three years from presumed cardiac insufficiency and arrhythmia.[5] Although mild hepatomegaly may be noted in those cases previously diagnosed,[5] it is most unusual for the reverse presentation to occur. This sequence of events is not to be confused with the cases reported by Naeye[6] and Levine[7] wherein the appearance of pulmonary hypertension developed subsequent to either intrahepatic disease or extrahepatic portal hypertension. Our patient

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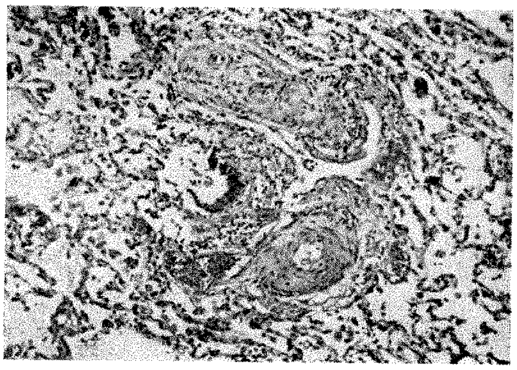

Fig. 1—Pulmonary arteries showing intimal and endothelial proliferation with concentric muscular hypertrophy (Hematoxylin and eosin, original magnification x430).

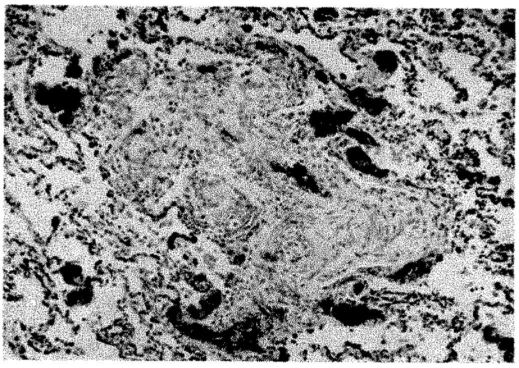

Fig. 2—Plexiform and angiomatoid lesions of severe primary pulmonary hypertension (Hematoxylin and eosin, original magnification x430).

had neither predisposing intrahepatic disease nor extrahepatic portal vein abnormalities which might produce portal hypertension from these sites.

## Case Report

A. P. was born of a 27-year old, gravida 2, para 2 mother following an uneventful pregnancy. Examination at birth revealed the following anomalies: mid line failure of closure of the cranium with exposure of the dura and saggital sinus; small right hand and shortened digits, the latter due to agenesis of the terminal phalanges; dysplastic nails of the hands and feet. Respiratory distress syndrome required the placement of an umbilical artery catheter. On the third day of life some grossly bloody stools were noted without abdominal distention or pneumatosis. At approximately 18 months of age, moderate abdominal distention was noted during a repeat episode of bloody stools. A prominent venous pattern was noted over the abdominal wall but no fluid wave could be elicited. The liver was felt 3 cm. below the costal margin and the spleen tip was palpable. A soft systolic murmur could be auscultated along the left sternal border. Esophagram was obtained and showed no esophageal varices but rather a pressure defect in the upper esophagus which subsequently proved to be an anomalous left subclavian artery arising from a right-sided aorta. Abdominal distention was noted by the attending physician on subsequent office visits, again without the presence of a fluid wave. At age two and a half years, mild hepatosplenomegaly was again noted and a systolic murmur was heard, again thought to be functional. A chest radiograph, urinalysis and chromosomal analysis were normal at this time. Following two weeks of abdominal distention, the patient suffered an episode of hematemesis, as well as a tonic seizure, necessitating admission to Denver Children's Hospital.

Pertinent physical findings were: temperature, 37° C; pulse, 136; respiration rate, 44; blood pressure, 84/72; height and head circumference, 50th percentile; weight, 80th percentile; congenital right parietal 4 × 5 cm. bony defect; periorbital edema; grade I/VI short ejection murmur at left sternal border and distended abdomen with a girth of 65 cm. A prominent fluid wave was detectable and the liver palpated 2 cm. below the right costal margin (span 8 cm.). The spleen was 3 cm. below the left costal margin and a prominent venous pattern

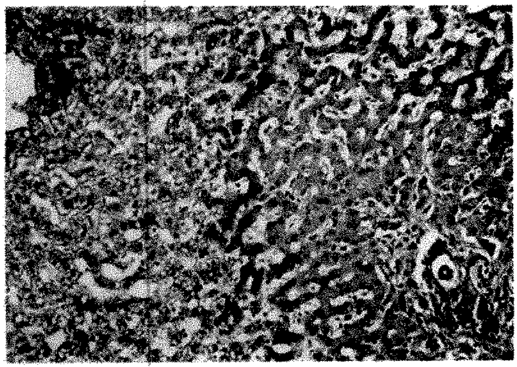

Fig. 3—Liver section shows changes of centrilobular congestion with moderate zonal steatosis. Portal and periportal areas (lower right) are normal (Hematoxylin and eosin, original magnification x440).

was also present. Dysplastic nails on the fingers and several toes were noted, as was microdactyly of the right hand. Icterus, liver palms, spider angiomata and digital clubbing were not found. Initial laboratory studies included hematocrit, 39.8; hemoglobin, 13.2; white blood count 12,100 with 79 segmented neutrophils, 1 band, 18 lymphocytes and 2 monocytes; 64,000 platelet count; prothrombin time, 16/12; partial thromboplastin time, 43/39; thrombin time, 12.5/8.5; fibrinogen, 165; negative fibrin split products; bilirubin, 2.8 indirect/3.6 total; alkaline phosphatase, 159 I.U.; SGOT, 48; LDH, 254.; BSP, 28%; BUN, 11; ammonia, 142; albumin, 2.5; total protein, 5.1; calcium, 4.6 mEq./l. The serum electrolytes and glucose values were normal. $HB_sAg$, RPR, alpha$_1$ antitrypsin, sweat test, ceruloplasmin, ANA were likewise normal. Right atrial hypertrophy, right ventricular hypertrophy—severe—and right axis deviation were present on EKG. Fluid obtained from a diagnostic peritoneal tap on the second hospital day contained protein of 272 mg.%, while amylase, BUN, chylomicrons and cell block were normal. Chest x-ray demonstrated mild cardiomegaly while abdominal films showed a large amount of peritoneal fluid with distended bowel loops. Large distal esophageal varices were demonstrated by esophagram. Liver-spleen scan showed uniformly poor liver uptake with normal spleen size.

Patient was placed on a regimen of salt and fluid restriction, spironolactone, chlorothiazide and salt-poor albumin and achieved a substantial diuresis. Cephalexin was begun on the fourth hospital day for an *E. coli* urinary tract infection. Several blood cultures yielded *Klebsiella* on the ninth hospital day with high unsegmented neutrophil count and thrombocytopenia of 14,000. This was treated successfully with carbenicillin and gentamicin and the child then underwent right heart catheterization using general endotracheal anesthesia. These studies demonstrated hepatic wedge pressure of 15 mm. Hg. (normal 5-8 mm. Hg.) with no gradient from this site to the right atrium. Wedged hepatic vein retrograde contrast injection showed normal sinusoidal reflux and no abnormalities in the hepatic venous systems. Contrast injected in the right atrium was observed to retrograde fill the main hepatic venous system. Right-sided cardiac pressures were in the systemic range (PA 86/47, RV 80-90/8, RA mean = 14) while femoral arterial pressure was 82/45. Cines revealed poor right ventricular contractility, the main pulmonary artery being markedly dilated, and "pruning" of peripheral pulmonic branches. During the attempt to measure pulmonary arterial wedge pressure, the patient developed bradycardia, 2:1 atrioventricular block and cardiopulmonary arrest. Vigorous attempts at resuscitation were unsuccessful and the patient expired.

Significant pathological findings noted at autopsy were the congenital anomalies described previously and those referable to the pulmonary and portal systems. Microscopic changes of severe irreversible pulmonary hypertension (grades 3-5 of Wagenvoort classification[8]) including recanalization of arteries, severely restricted lumens due to endothelial proliferation and medial hypertrophy. Angiomatoid plexiform lesions were frequently noted (Figs. 1 and 2). There was no evidence of fresh thrombi or emboli. The right ventricle was markedly dilated with hypertrophy of the muscular layers. The hepatic pathology was consistent with recent congestion showing post-sinusoidal dilatation, centrilobular necrosis without fibrosis or regenerating nodules (Fig. 3). Careful dissection of the extrahepatic portal vein revealed patency in its entirety. No abnormal portovenous communication was found. Moderate splenomegaly and distal esophageal varices were also present.

## COMMENT

We believe this patient illustrates an unusual presentation of primary pulmonary hypertension. This condition needs to be considered in the differential diagnosis of unexplained portal hypertension. Signs of right heart failure manifested by mild hepatomegaly have been noted by other workers but the presence of recurrent episodes of ascites has not been mentioned.[5] In this particular child, cardiorespiratory symptoms were not present until she was terminal. Indeed, the low index of suspicion that primary pulmonary hypertension existed probably contributed to her early demise. It has been known for some time that the potential for fatal complications during or immediately after cardiac catheterization studies in these patients is alarmingly high.[5, 9]

In the reported cases wherein co-existing pulmonary and portal hypertension has been documented, underlying hepatic or portal vein pathology has always been found.[6, 7] It has been suggested that in the face of chronic liver disease, circulating humoral substances escaping hepatic detoxification may produce pulmonary arterial vasospasm. Children, lacking the number of muscular-walled arteries of adults, may have a different susceptiblity to vasoconstrictive substances acting on the pulmonary vasculature.[7, 10] In light of the significant number of congenital anomalies present in this patient, one might speculate that host vulnerability to these circulating agents may have played an additional but unknown role.

Thrombosis of the extrahepatic portal vein (with or without intrinsic liver disease) has been reported in association with pulmonary hypertension. It is believed that microemboli shed within these venous channels then reach the pulmonary circulation by portasystemic shunts and are responsible for the subsequent development of pulmonary hypertension.[7] Although our patient presented with thrombocytopenia, splenomegaly and developed evidence of platelet consumption during *Klebsiella* bacteremia, fibrin-split products were never never found and normal coagulation function was quickly restored with antibiotics. Furthermore, microthrombi or new fibrin deposition was not detected by microscopic study of the autopsy material.

It would appear that primary pulmonary hypertension was responsible for producing progressive portal hypertension in this child. A most compelling explanation stems from the catheterization results where elevated pressures (systemic) from the pulmonary arteries to the hepatic veins were found, while other known mechanisms for pulmonary hypertension were excluded by the autopsy results.[1, 11, 12]

## SUMMARY

This case report demonstrates the primary role of pulmonary hypertension producing advanced suprahepatic portal hypertension in a two and a half-year old female.

A careful investigation did not yield previously recognized causes of portal hypertension. We believe this is the first reported case of this entity.

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# The Radiology Corner*

## HEPATIC ABSCESS—PLAIN FILM FINDINGS AS AN EARLY AID TO DIAGNOSIS

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### INTRODUCTION

Pyogenic abscess of the liver still remains a disease of high mortality. The apparent reason is that the disease usually goes unrecognized because of delay in appropriate diagnostic procedures.[1] Roentgenographic examination plays a major role in the evaluation of hepatic abscess, with early plain film changes, at times, suggesting the diagnosis. Two cases of pyogenic liver abscess in which the diagnosis was strongly suggested by the presence of a gas collection overlying the hepatic silhouette are reported to demonstrate the value of plain films.

### CASE REPORTS

*Case 1:*—A 59-year old black woman was admitted for evaluation of fever of unknown etiology. One week prior to admission the patient was treated symptomatically for a nonspecific febrile illness felt to be an acute viral syndrome. Persistent fever with progressive malaise, anorexia and weight loss, however, necessitated hospitalization. On admission she was lethargic with temperature of 39.3° C; blood pressure, 110/80; respirations, 24/min.; pulse, 100/min. There was slight scleral icterus. The abdomen was soft with guarding localized to an ill-defined area of fullness in the right epigastrium. The packed cell volume was 33.7%; white blood count, 14,400; bilirubin, 3.4 mg.% total, 2.6 mg.% direct; alkaline phosphatase, 136 mU./cc.; SGOT, 26 mU./ml. Presumptive diagnosis was acute cholecystitis. An erect frontal plain roentgenogram of the abdomen (Fig. 1) revealed two unusual air fluid levels lying centrally in the upper abdomen. An erect lateral roentgenogram demonstrated that the two air fluid levels were located arteriorly. An upper gastrointestinal barium study showed that the central collections of air did not arise from or communicate with the stomach or duodenum. A delayed erect film of the upper gastrointestinal series demonstrated that the air bubbles were unrelated to the colon. These two views demonstrated that the air was extraintestinal. A $^{99m}$Tc sulfur colloid liver scan (Fig. 2) showed a large intrahepatic defect in the region of the quadrate lobe and medial segment of the liver. Gallium citrate $^{67}$ Ga scan demonstrated an increased area of uptake in the same region of the liver that exhibited a defect in the Technetium scan. Antibiotic coverage with clindamycin, kanamycin and metronidazole was instituted. Amebic hemagglutination titer was negative. Four days following the gallium scan, the patient was taken to surgery at which time incision and drainage of a large abscess of the left lobe of the liver

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[*] Edited by Richard H. Marshak, M.D., F.A.C.G. and Arthur E. Lindner, M.D., F.A.C.G.
From the University of Miami School of Medicine.

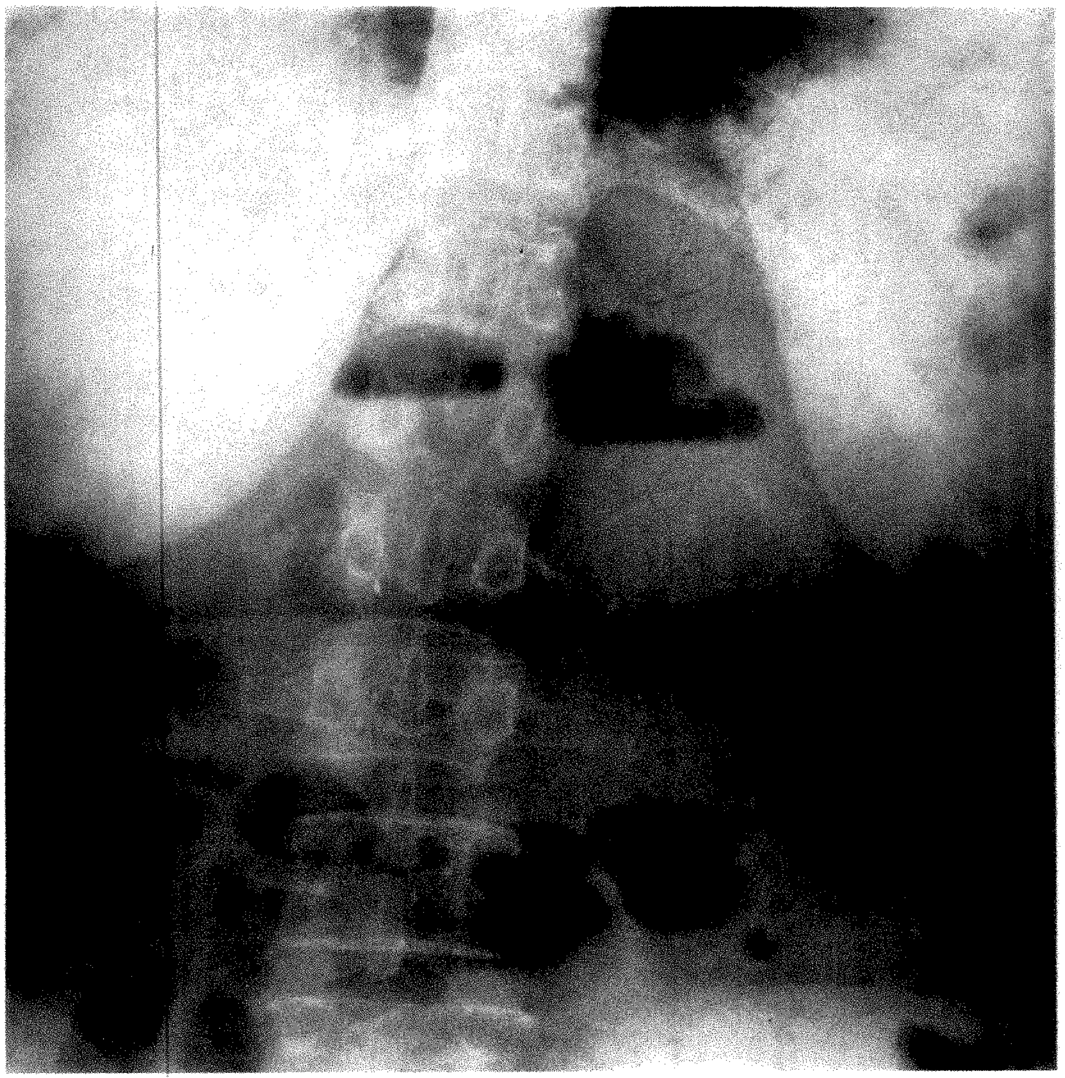

Fig. 1—An erect frontal roentgenogram reveals two unusual air fluid levels lying centrally in the upper abdomen. The air-filled transverse colon appears to lie inferiorly.

was performed. Foul smelling purulent material was obtained of which subsequent aerobic and anaerobic cultures remained negative. The patient improved during an uneventful postoperative course.

*Case 2:*—A 58-year old black female was admitted for a change in mental status. She had been well until two days prior to admission when she experienced nausea, vomiting and generalized abdominal pain. On the day of admission her family noted an altered mental status and urinary incontinence. Past medical history was unremarkable. On admission she was markedly lethargic but oriented. Temperature, 41° C; blood pressure, 80/60; pulse, 120/min.; respirations, 40/min. The abdomen was soft with epigastric and right upper quadrant tenderness and no hepatomegaly. Packed cell volume was 43%; white blood count, 1,500; total bilirubin, 2.4 mg.%; alkaline

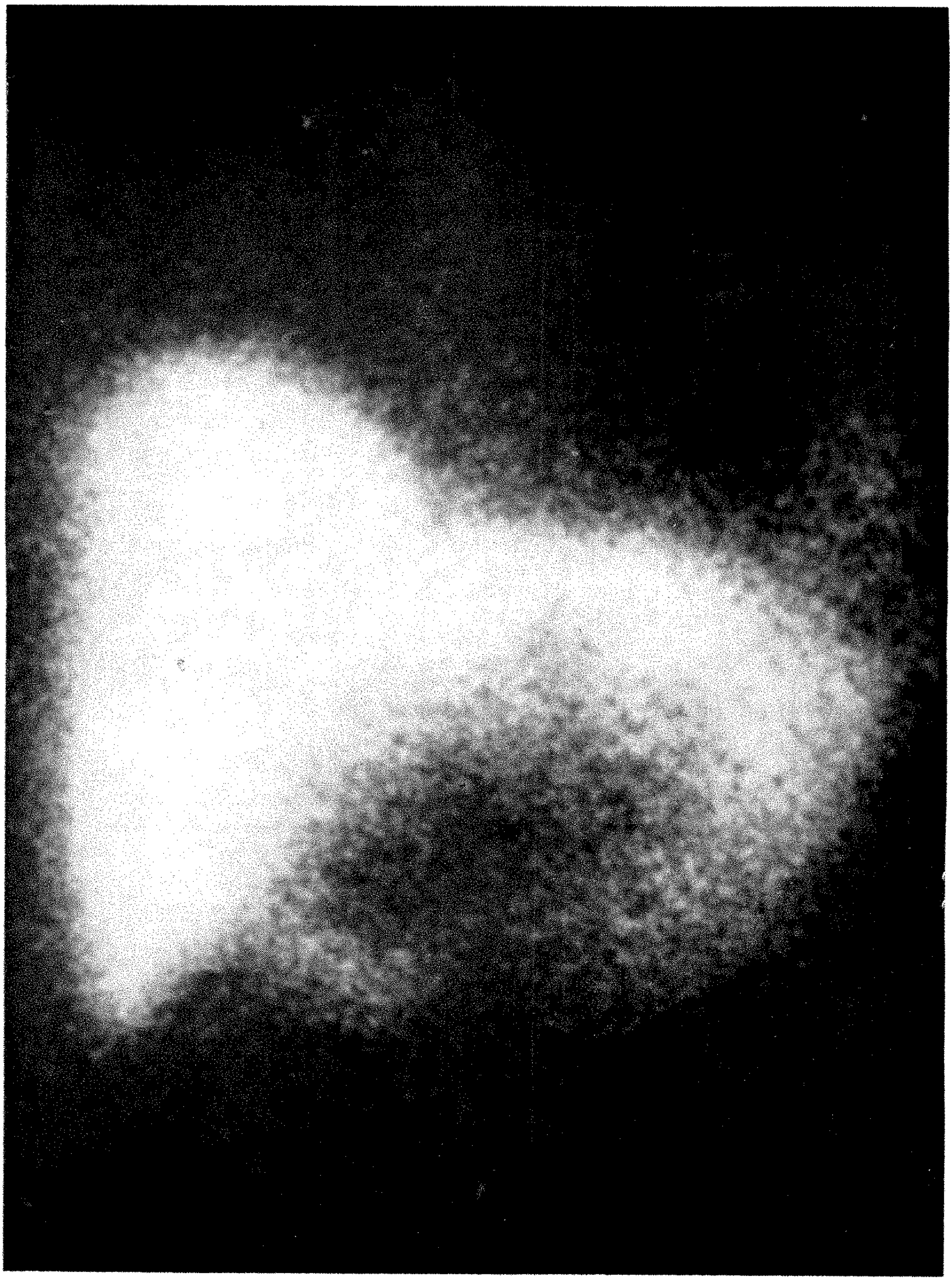

Fig. 2—A $^{99m}$Tc sulfur colloid scan shows a large defect in the region of the quadrate lobe and medial segment of the liver.

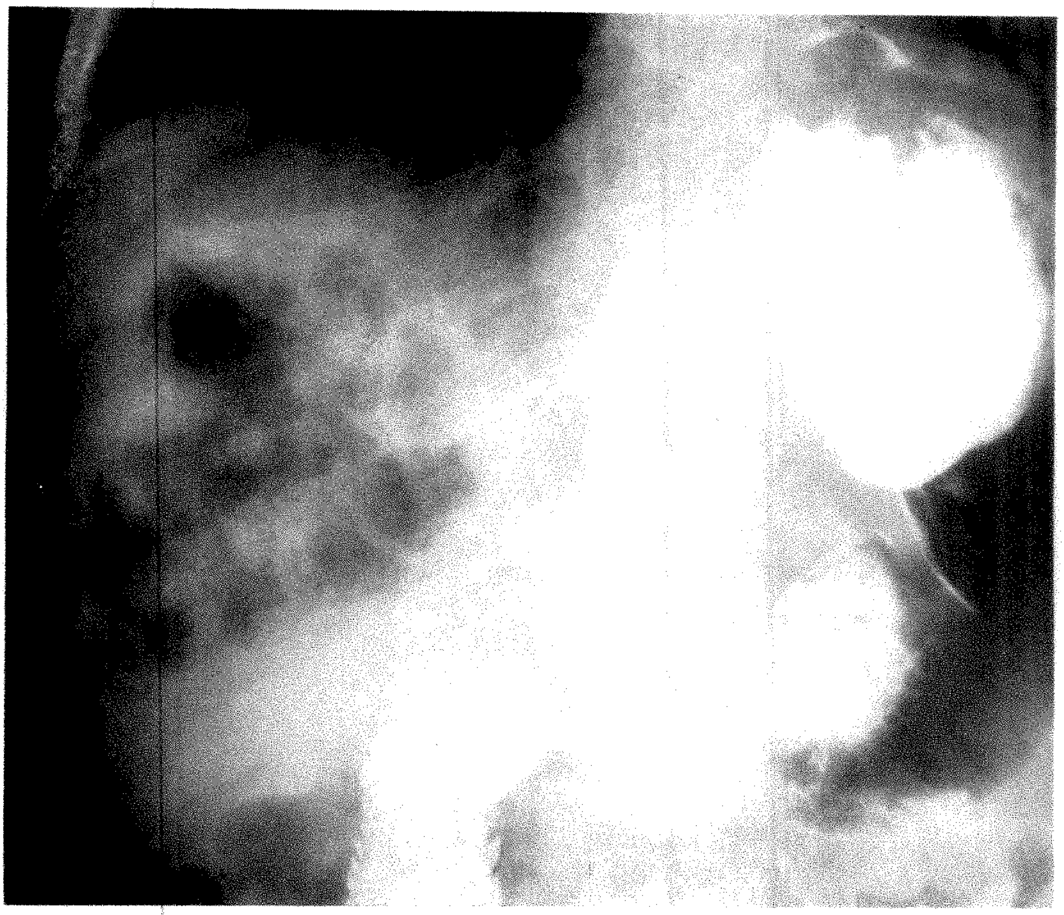

Fig. 3—Multiple small air bubbles are seen in a well-localized area of the right upper quadrant on this roentgenogram of an upper gastrointestinal series. This small bubbly appearance is another pattern of abscess that may be seen on plain roentgenograms of the abdomen.

phosphatase, 183 mU./ml.; SGOT 332 mU./ml. Chest radiograph revealed an air-fluid level behind the cardiac silhouette consistent with hiatal hernia and air in the right upper quadrant felt to be colonic. Spiking fevers persisted and *Klebsiella* was isolated in three blood cultures. Antibiotic coverage with Keflin® and Gentamycin® was instituted. A subsequent abdominal plain film demonstrated a large collection of mottled air in the right upper quadrant. An upper gastrointestinal barium study (Fig. 3) demonstrated the multiple small air bubbles well localized to the right upper quadrant. A liver scan revealed a large space-occupying defect in the posterior aspect of the right lobe of the liver. Laparotomy was performed and a large air-fluid filled cavity was found involving the posterolateral right hepatic lobe. The abscess was drained and *Klebsiella* was isolated from its contents.

## COMMENT

The diagnosis of pyogenic hepatic abscess has been greatly facilitated by the hepatic scintiscan which has been shown to demonstrate lesions greater than 2 cm. in size with a 95% accuracy rate.[2] Hepatic ultrasonography,[3, 4] $^{67}$Ga (gallium citrate) scan[5] and angiography[6] have all been shown to add to the diagnostic accuracy. At the time of initial presentation, however, roentgenographic observations can be valuable in suggesting the presence of an intrahepatic suppurative process. The chest roentgenogram may be abnormal in approximately 50% of patients with hepatic abscess.[1] Roentgenographic evidence of diaphragmmatic involvement characteristically includes elevation, loss of movement and altered contour of the right hemidiaphragm. Findings, such as pleural effusion, atelectasis or pneumonitis,[7] may also be present in the right lung base.

Another presenting feature may be the presence of an unusual collection of gas on the plain film. The first step in the diagnosis of an unusual collection of gas in the abdomen is its localization with frontal and lateral plain films. Gas seen to lie anteriorly in the upper abdomen excludes renal, perirenal, or retroperitoneal gas, which lie posteriorly. Emphysematous cholecystitis can usually be excluded when the characteristic pear-shaped shadow of gas in the gallbladder is not evident. Intravenous cholangiography may be needed for further clarification of the state of the biliary tree.

The next consideration is that the gas may communicate with the gastrointestinal tract, either because of a perforated viscus or because of an unusual diverticulum. Outlining the stomach and duodenum with barium and following the contrast material through the colon therefore comprise the next radiologic maneuver.

The roentgenographic finding of air or air fluid levels in hepatic parenchyma appears when breakdown of tissue occurs in the presence of gas-forming bacteria. The presence of gas in pyogenic intrahepatic abscesses is distinctly uncommon. In their review of the literature Foster, Schneider and Seaman[8] noted only eight reported cases and since then several other reports have appeared in the literature.[1, 6, 9, 10]

The radiographic finding of a collection of gas in the region of the liver should bring to mind several diagnostic considerations. Subphrenic and infrahepatic abscesses are the most common causes but, at times, may be difficult to distinguish from an intrahepatic abscess. Air fluid levels in close proximity to the diaphragm may support the diagnosis of a subphrenic abscess. Combined liver and lung scanning can be helpful in further defining a suspected subphrenic abscess. To distinguish subhepatic (or infrahepatic) abscess[11] from intrahepatic abscesses[12] an isotope liver scan or an ultrasound examination will provide more definitive localization. In some cases, however, a peripheral liver defect is visualized and hepatic arteriography will be needed to decide whether the mass is intrahepatic, or extrahepatic and compressing the liver.[12]

This report describes two patients with an unusual gas pattern on plain films and reinforces the idea that plain film findings may give an early clue to the diagnosis of hepatic abscess.

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# The Last Page

## QUESTIONS IN GASTROENTEROLOGY

CHARLES G. HAZZI, M.D., F.A.C.P., F.A.C.G.*
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*The Last Page* appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the article can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. ENDOSCOPY IN ATROPHIC GASTRITIS:

   A. Criteria used are visibility of submucosal blood vessels, discoloration and smoothness of the mucosa.

   B. Visible submucosal vessels may be found in up to 13% of patients with upper gastrointestinal symptoms.

   C. This indicates atrophic gastritis whether the findings are patchy or diffusely distributed.

   D. Fiberoptic endoscopes may allow more frequent visualization of submucosal vessels than older gastroscopes.

   (Page 376)

2. DYE CLEARANCE IN ROTOR'S SYNDROME:

   A. There is nonvisualization of the gallbladder as in the Dubin-Johnson syndrome due to the same defect in handling the contrast medium.

   B. There is marked reduction in BSP and indocyanine green clearance, with the same late rise in plasma levels as in the Dubin-Johnson syndrome.

   C. There is decreased hepatic BSP uptake (Tm) and storage, unlike the D-J syndrome, as well as disturbed excretory function.

   D. Clearance of injected unconjugated bilirubin is also depressed.

   (Page 380)

3. PHENOXYBENZAMINE (POB) AND PORTAL VEIN PRESSURE:

   A. POB is a beta adrenergic receptor blocking agent.

   B. POB lowers vascular resistance but not in the cerebral and coronary vascular beds.

   C. When injected in patients with portal hypertension, POB lowered mean portal vein pressure by approximately 78%.

   D. Pretreatment with POB does not prevent ischemic liver damage.

   (Page 389)

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* Associate Professor of Clinical Medicine, New York University School of Medicine.

4. MONILIAL ESOPHAGITIS:

A. Usually affects cancer patients on chemotherapy or patients receiving corticosteroids or antibiotics.

B. Is as commonly due to *Torulopsis glabrata* as to *Candida* species.

C. Is the only reported manifestation of *Torulopsis glabrata* infection.

D. May be treated with oral Mycostatin.

(Page 395)

5. SQUAMOUS PAPILLOMA OF THE ESOPHAGUS:

A. Is as common as in other squamous epithelial surfaces.

B. Has been shown to be due to a viral agent.

C. May be multiple and usually occurs in the middle or distal third.

D. May be confused with verrucous carcinoma unless biopsied or resected.

(Page 398)

6. GRANULAR CELL TUMOR OF COMMON BILE DUCT:

A. Is not as common as in the tongue.

B. Has been described only in Caucasians.

C. Is usually a benign tumor in this and other primary sites.

D. Is composed of polygonal cells with eosinophilic cytoplasm containing multiple coarse PAS positive granules.

(Page 401)

7. CHOLEDOCHAL CYST:

A. Usually presents a triad of pain, jaundice and palpable RUQ mass.

B. May be complicated by cholangitis, liver abscess or portal vein thrombosis.

C. Is often associated with recurrent pancreatitis.

D. Is best treated by choledochocystojejunostomy.

(Page 408)

8. OBSTRUCTION OF THE MAIN PANCREATIC DUCT:

A. When this is complete on ERCP, it always indicates carcinoma.

B. Cytology of the pancreatic juice in malignant duct occlusion in the body and tail of the pancreas has a high yield.

C. Scintigraphy and sonography easily distinguish between inflammatory and malignant duct obstruction.

D. Sonographic guided percutaneous needle biopsy of the pancreas is a valuable procedure in such cases.

(Page 412)

9. ILEOVESICAL FISTULA:

A. Is more common than colovesical fistula.

B. Is more commonly due to tumor than to regional enteritis.

C. Will always close after total parenteral nutrition.

D. May be diagnosed by detecting in the urine orally administered 14C polyethylene glycol, when barium studies and cystoscopy fail.

(Page 415)

10. MALROTATION OF THE DUODENUM:

A. This is always associated with malrotation of the colon.

B. Duodenal rotation is completed at the 10th week of fetal life.

C. Both duodenal and colonic rotation are anticlockwise.

D. Duodenal obstruction due to malrotation occurs in the third portion of the duodenum.

(Page 421)

11. PATHOGENESIS OF PANCREATITIS:

A. Pancreatitis may occur in patients without a common channel and does not occur in all patients with a common channel.

B. The mechanistic theory of pancreatitis assumes stimulation of the gland against obstruction, resulting in ductular rupture.

C. Chronic alcohol ingestion leads to pancreatic hypersecretion.

D. The pancreas in alcoholics shows the same range of histologic changes as does the liver.

(Page 424)

12. PULMONARY AND PORTAL HYPERTENSION:

A. Suprahepatic portal hypertension may be due to hepatic vein occlusion, constrictive pericarditis or congestive heart failure.

B. Primary pulmonary hypertension does not cause portal hypertension.

C. Chronic liver disease may cause humorally-mediated pulmonary hypertension.

D. In portal vein thrombosis, shedding of microemboli may result in pulmonary hypertension.

(Page 427)

13. PLAIN X-RAYS FINDINGS IN HEPATIC ABSCESS:

A. The chest roentgenogram may show diaphragmatic, pleural or pulmonary abnormalities in 50% of patients.

B. A gas collection due to liver abscess lies posteriorly on lateral plain films.

C. Gas in subphrenic or subhepatic abscesses is easily distinguished from hepatic abscess on plain films.

D. Barium studies are needed to exclude gas communicating with the gastrointestinal tract.

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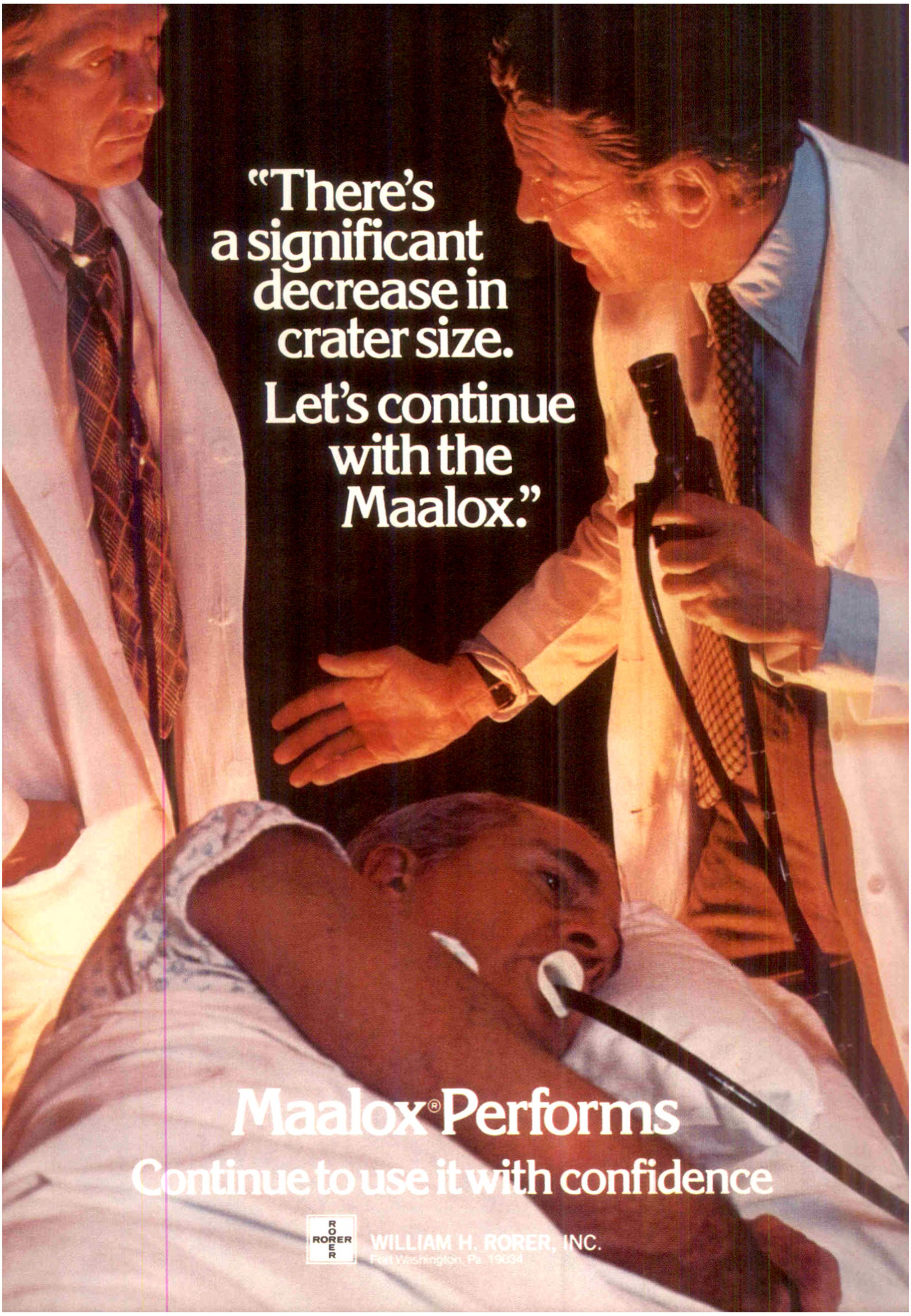
## ERRATA

In the article "BCG Treatment of Crohn's Disease" by Said Rahban, M.D., et al., which appeared on pages 196-201 of our February, 1979 issue, two typographical errors occurred.

In the right hand column of Table I on page 198, the figures for PHA should have read: 33,741 ± 4,234.

Also on page 198, on the third line from the bottom of the left hand column it should have read: per minute ± SEM.

We apologize for these errors and the necessary corrections have been made in the reprints.



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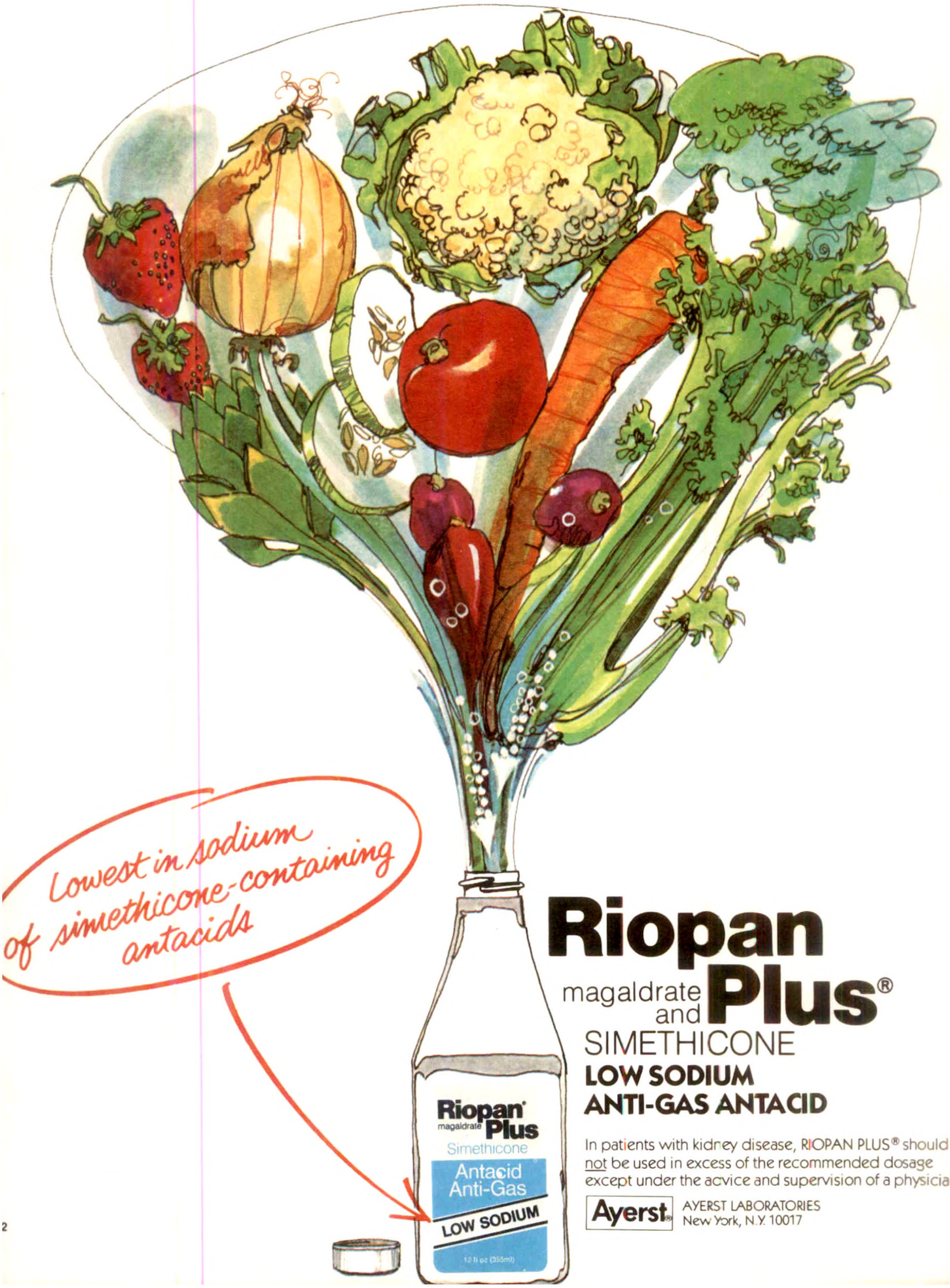
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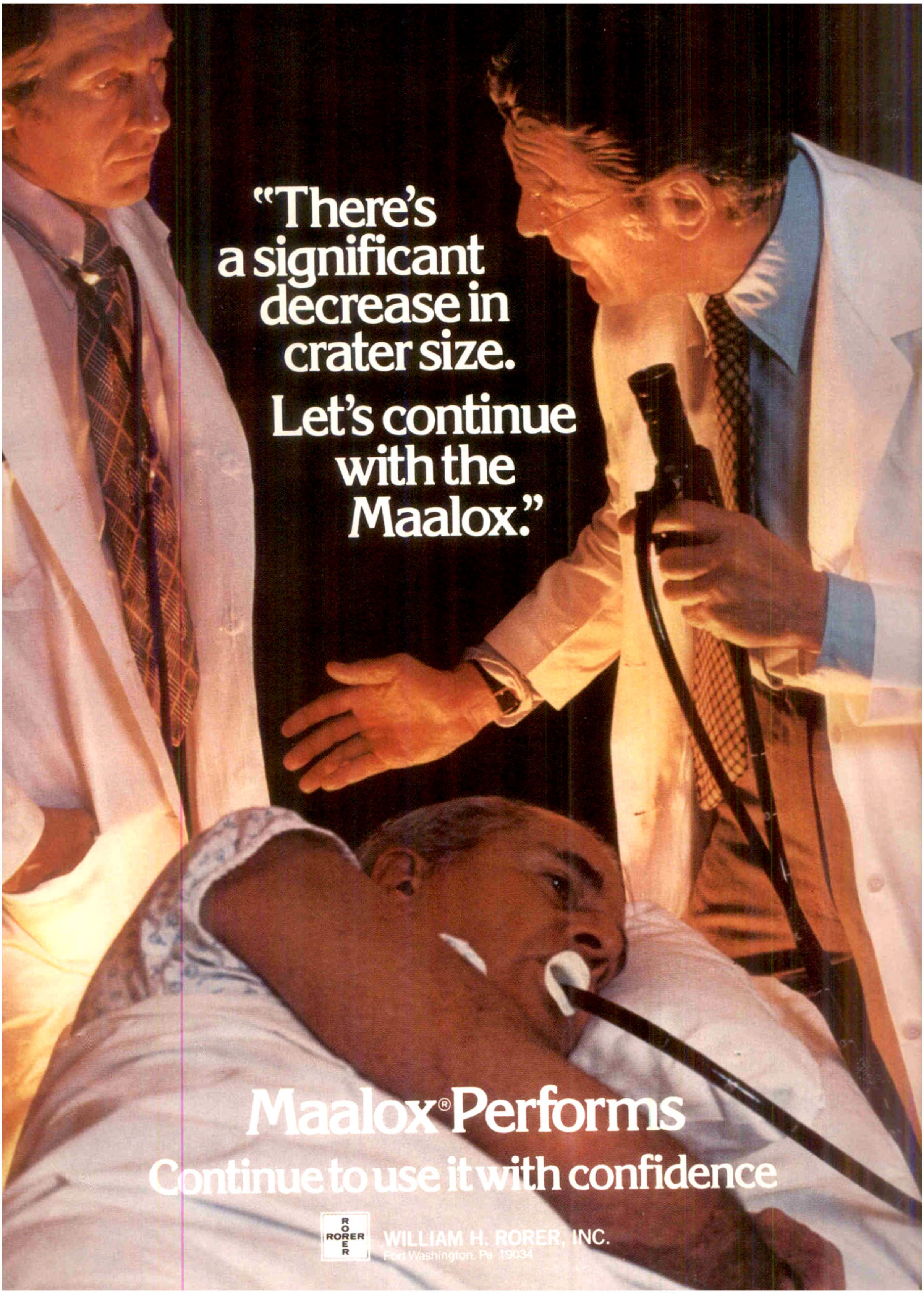
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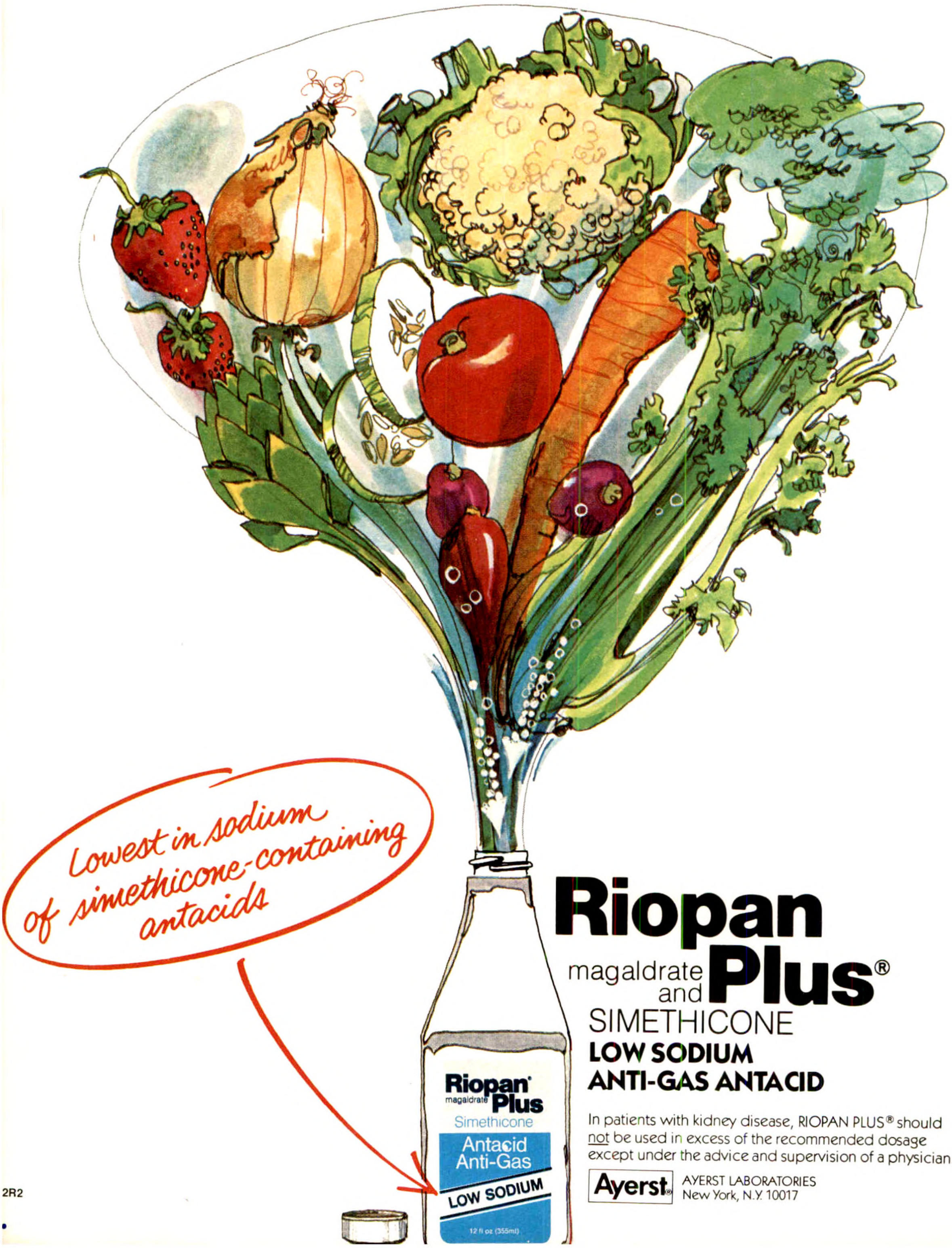
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# The American Journal of Gastroenterology

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*The Pioneer Journal of Clinical Gastroenterology, Proctology and Allied Subjects in the United States and Canada*

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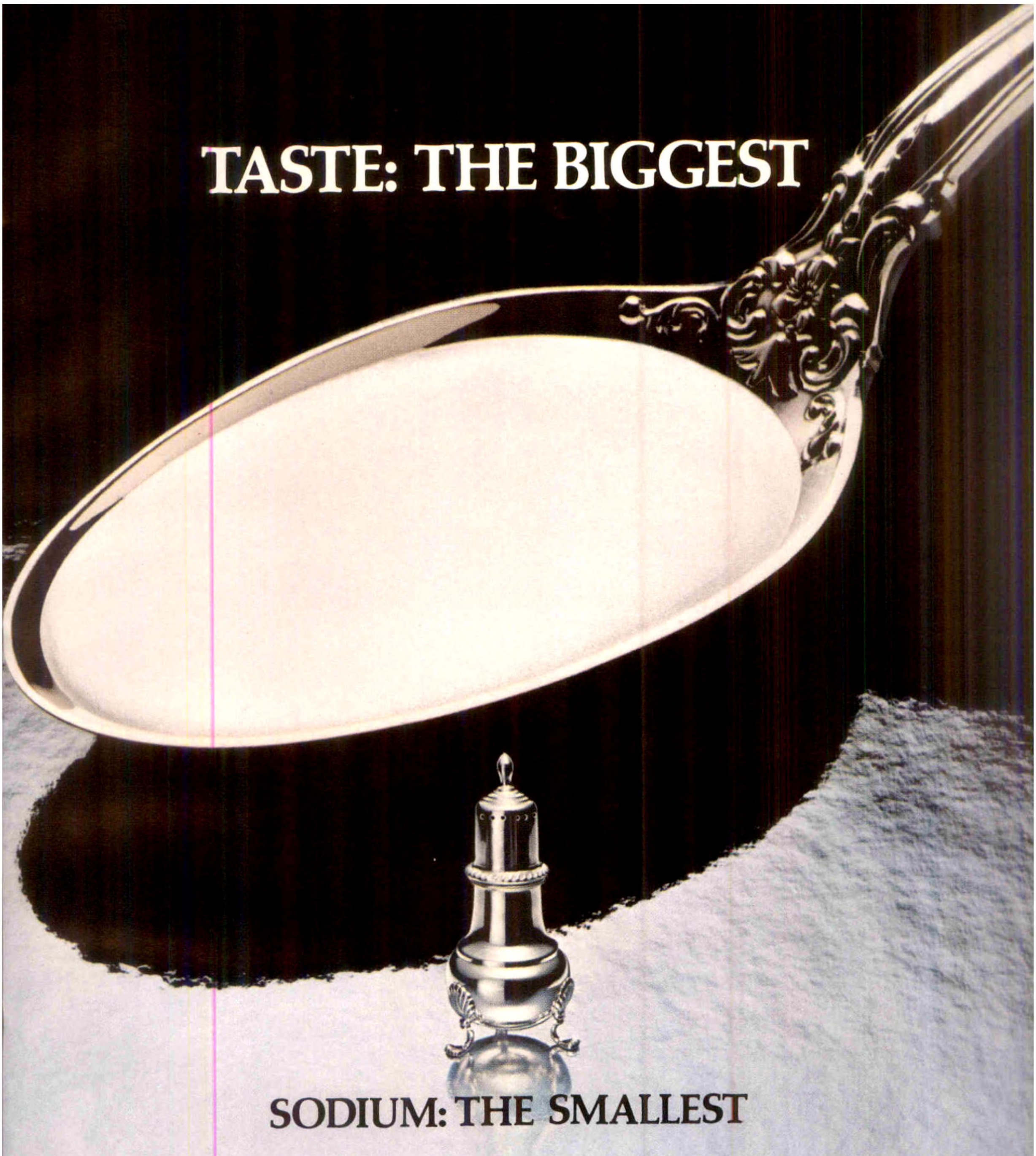

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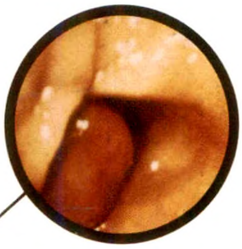

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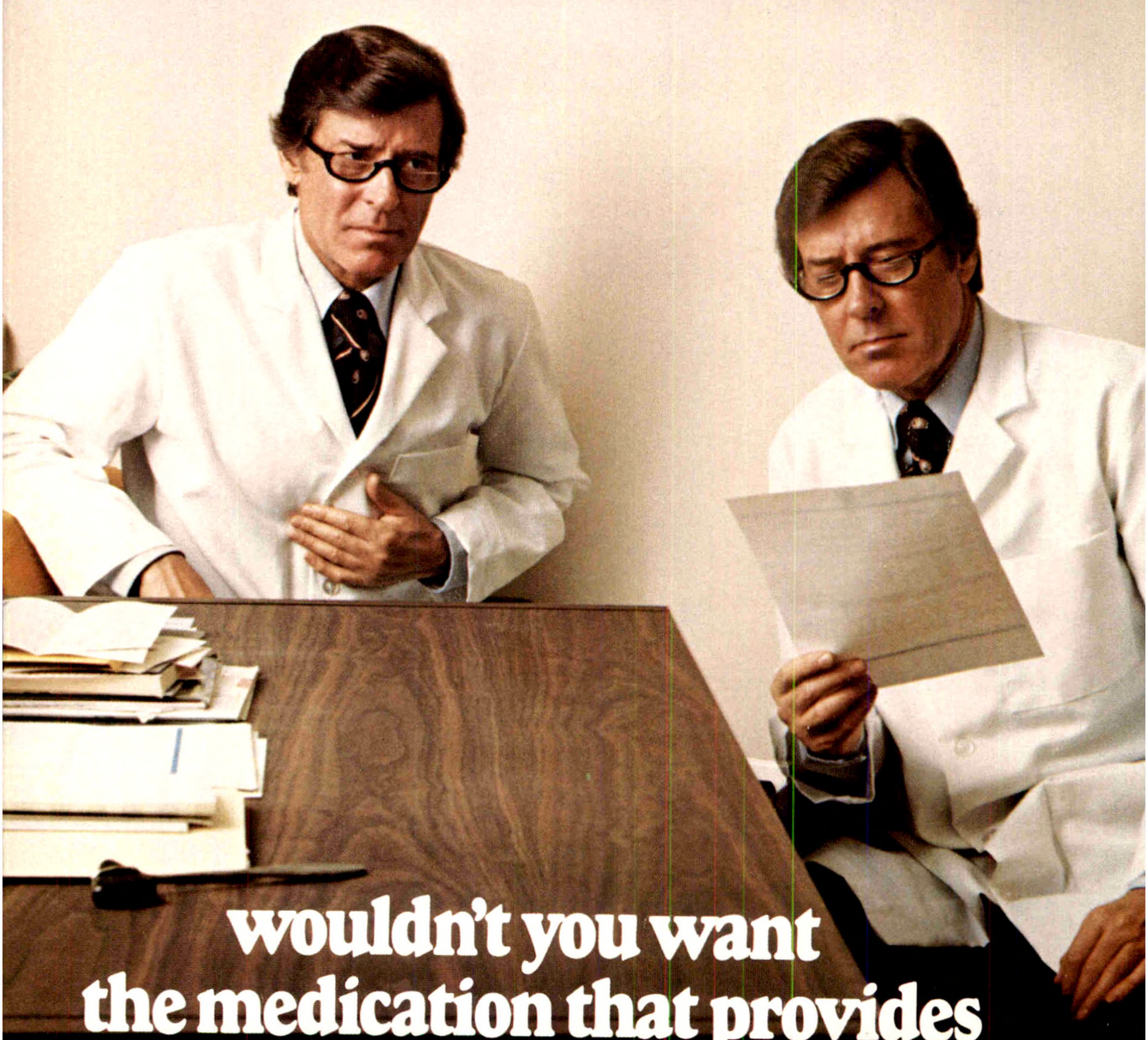

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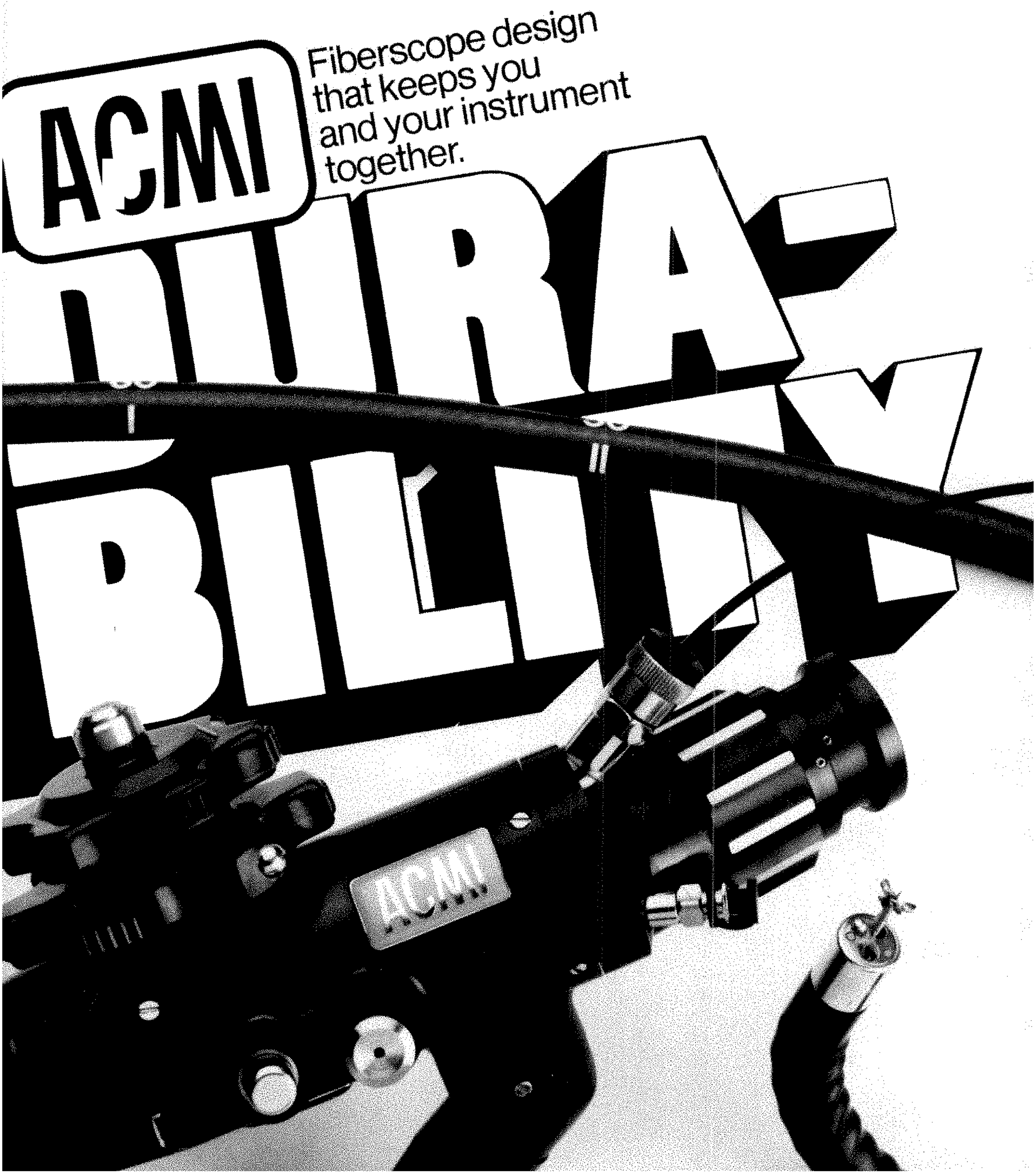
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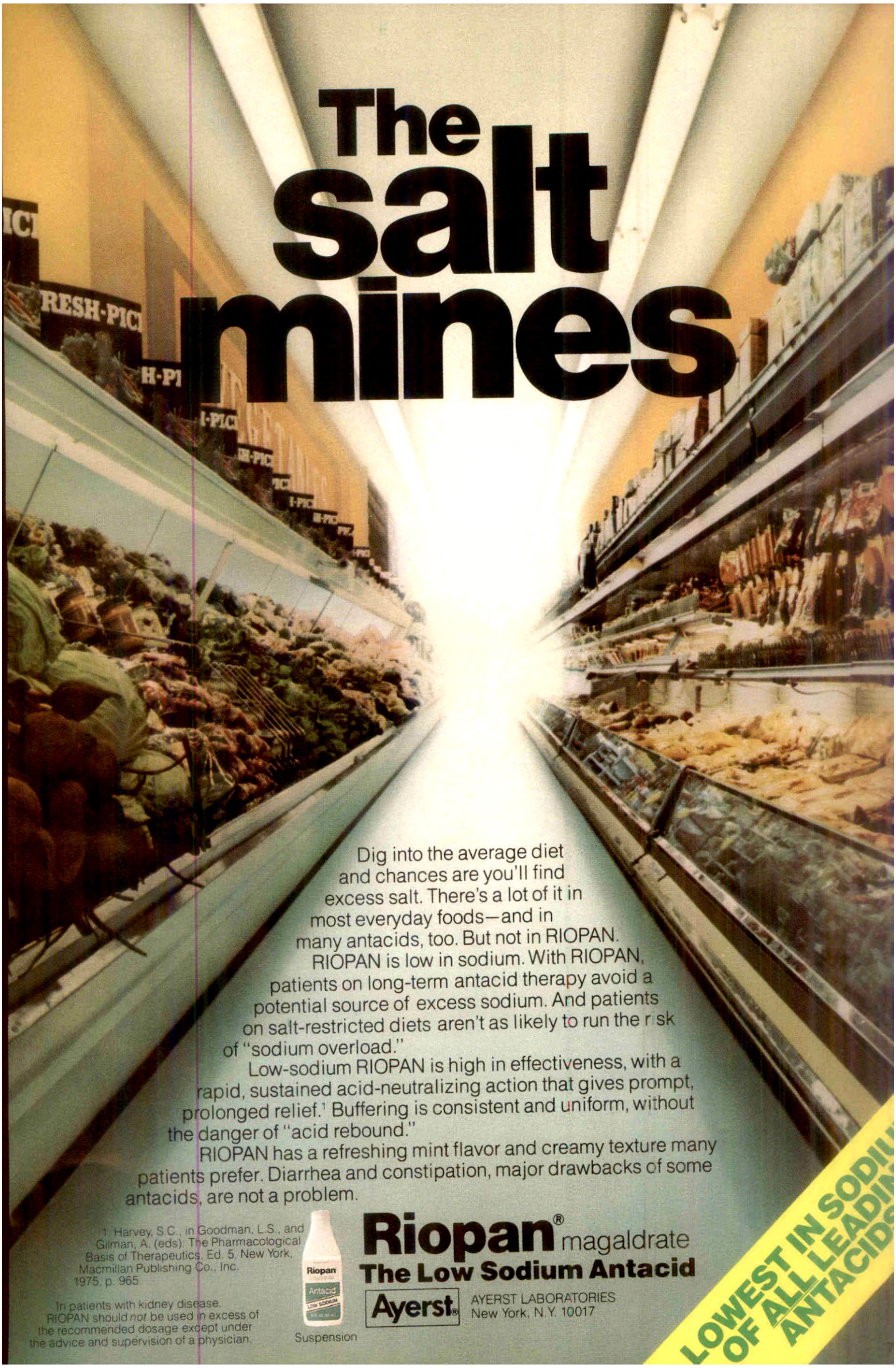

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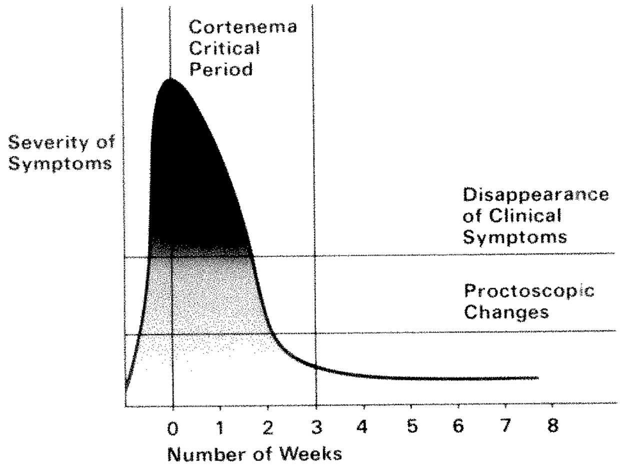

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See page opposite for brief summary.

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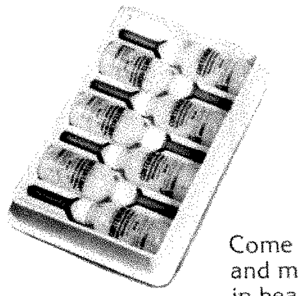

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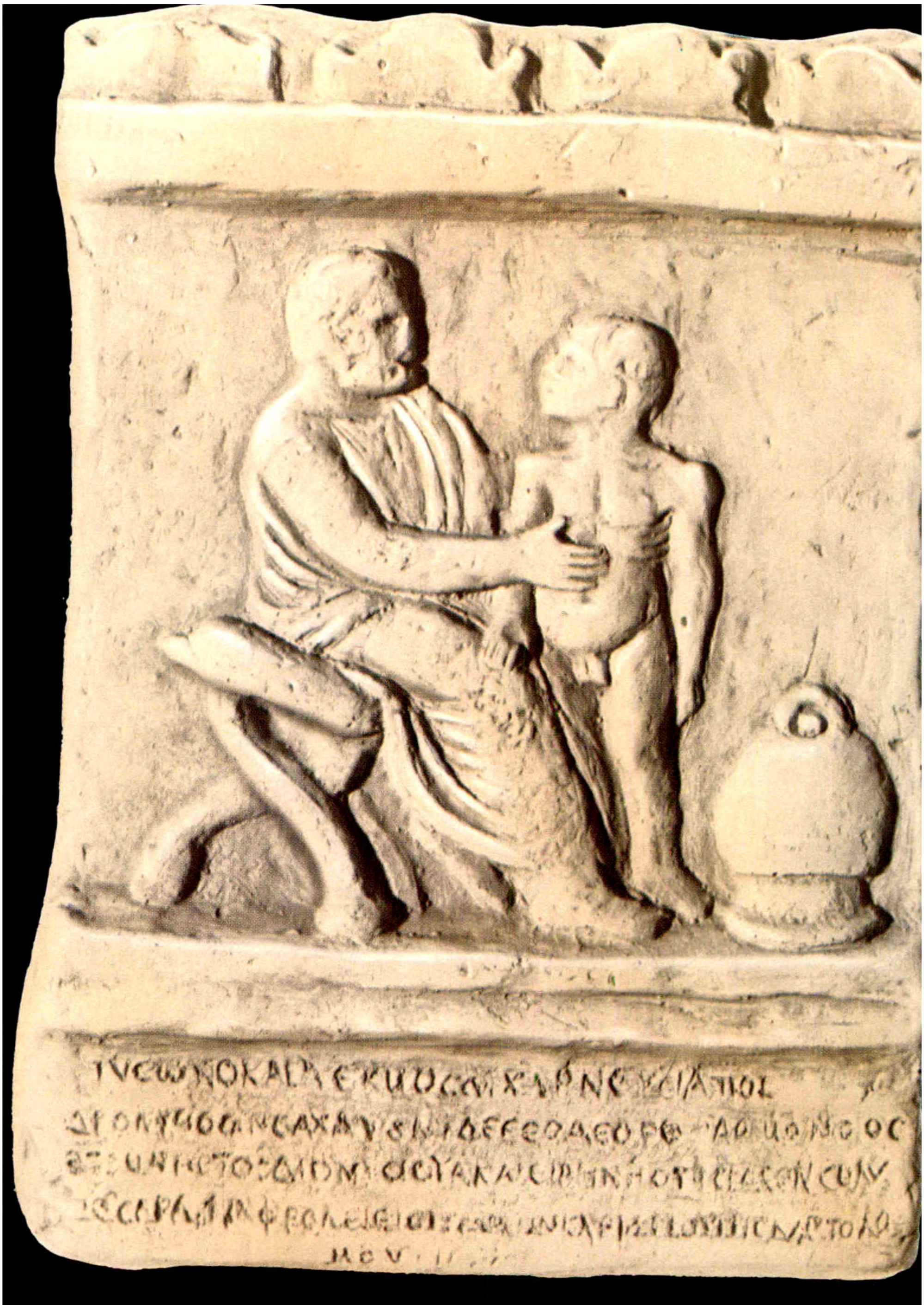

Illustrated is a replica of the classic stone carving of the Athenian Doctor, Jason, engaged in a palpatory examination of his patient's gastrointestinal tract—possibly the first evidence of a physician's special interest in gastroenterology.

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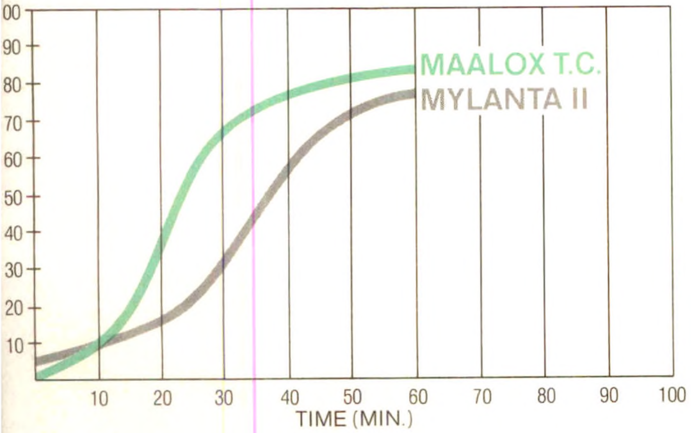

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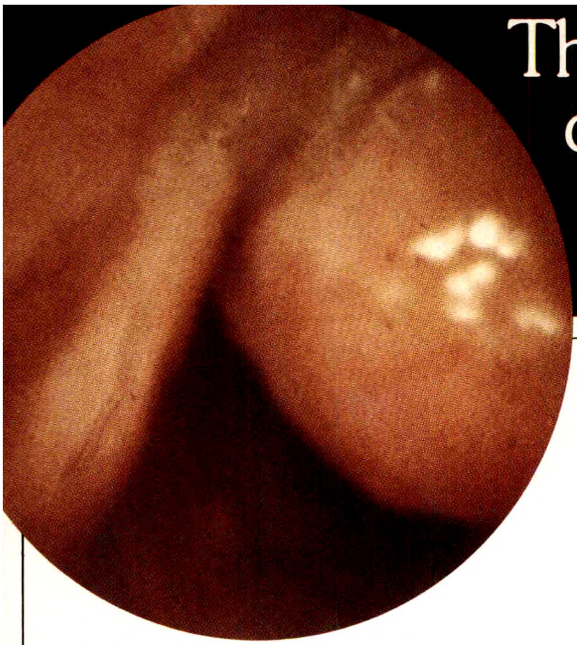

# The patient has dysphagia of 1½ years' duration.

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X-ray studies are inconclusive.

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*Esophagoscopy* was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

# Endoscopy

## -confirmatory or contradictory-

# a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

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**4 The convenience and economy of a single Rx** help sustain patient compliance, while providing relief of both emotional and somatic symptoms.

## A distinctive antianxiety-antispasmodic agent

# Librax®

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**Please consult complete prescribing information, a summary of which follows:**

**Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

**Contraindications:** Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

**Precautions:** In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

**Adverse Reactions:** No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

**Dosage:** Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

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## MEETINGS OF INTEREST

**44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.**

**Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.**

**Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.**

International Symposium on Infant Nutrition and the Development of the Gastrointestinal Tract, State University of New York at Buffalo, Department of Pediatrics and Children's Hospital, Buffalo, Niagara Hilton, Niagara Falls, NY, 3-8 June 1979.

Frontiers of Science and the Liver—A Symposium, In Honor of the 75th Birthday of Hans Popper, M.D., F.A.C.G. (Hon.), Mount Sinai School of Medicine of the City University of New York, 1 Gustave Levy Place, New York, N. Y., 5 June 1979.

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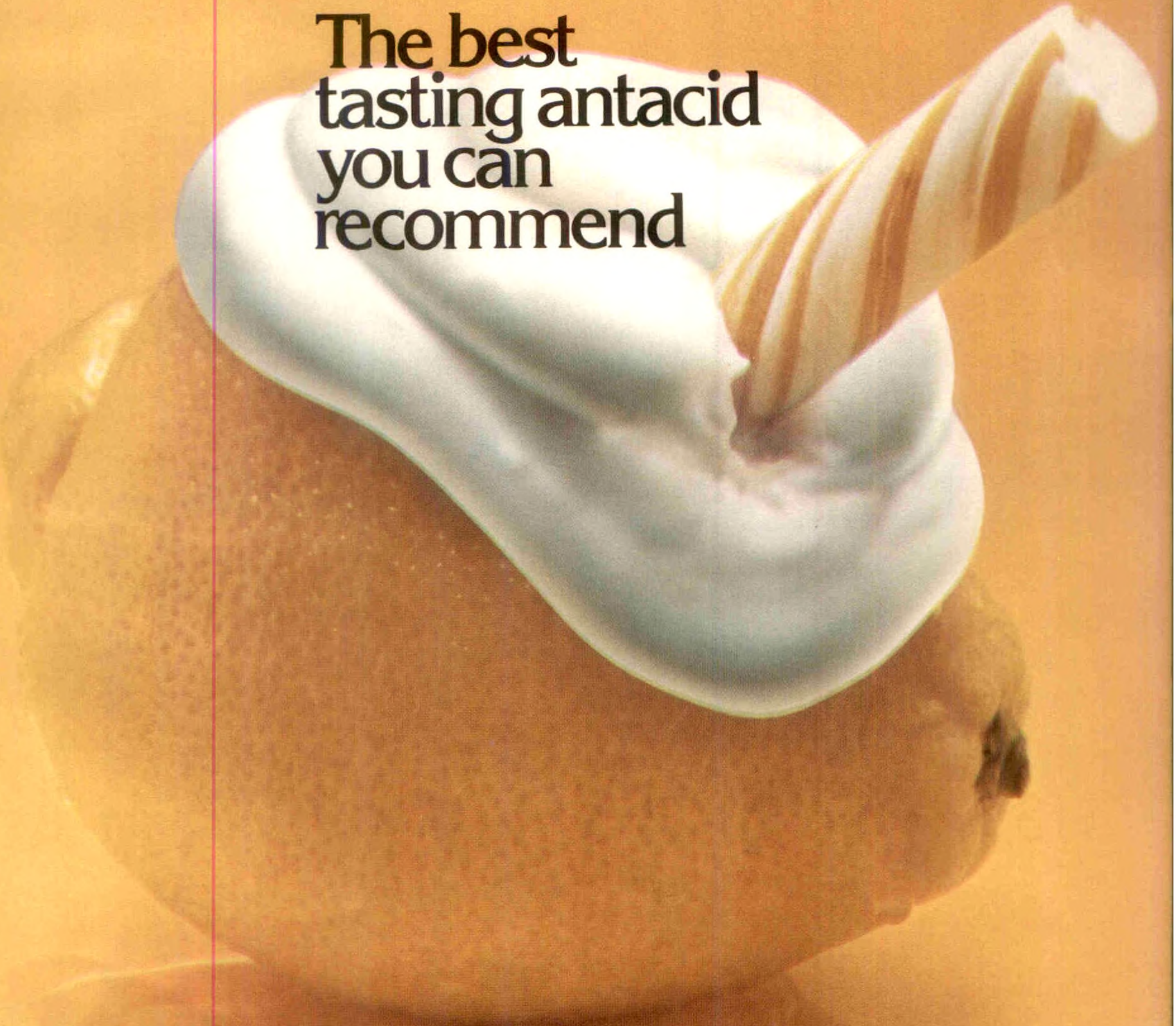

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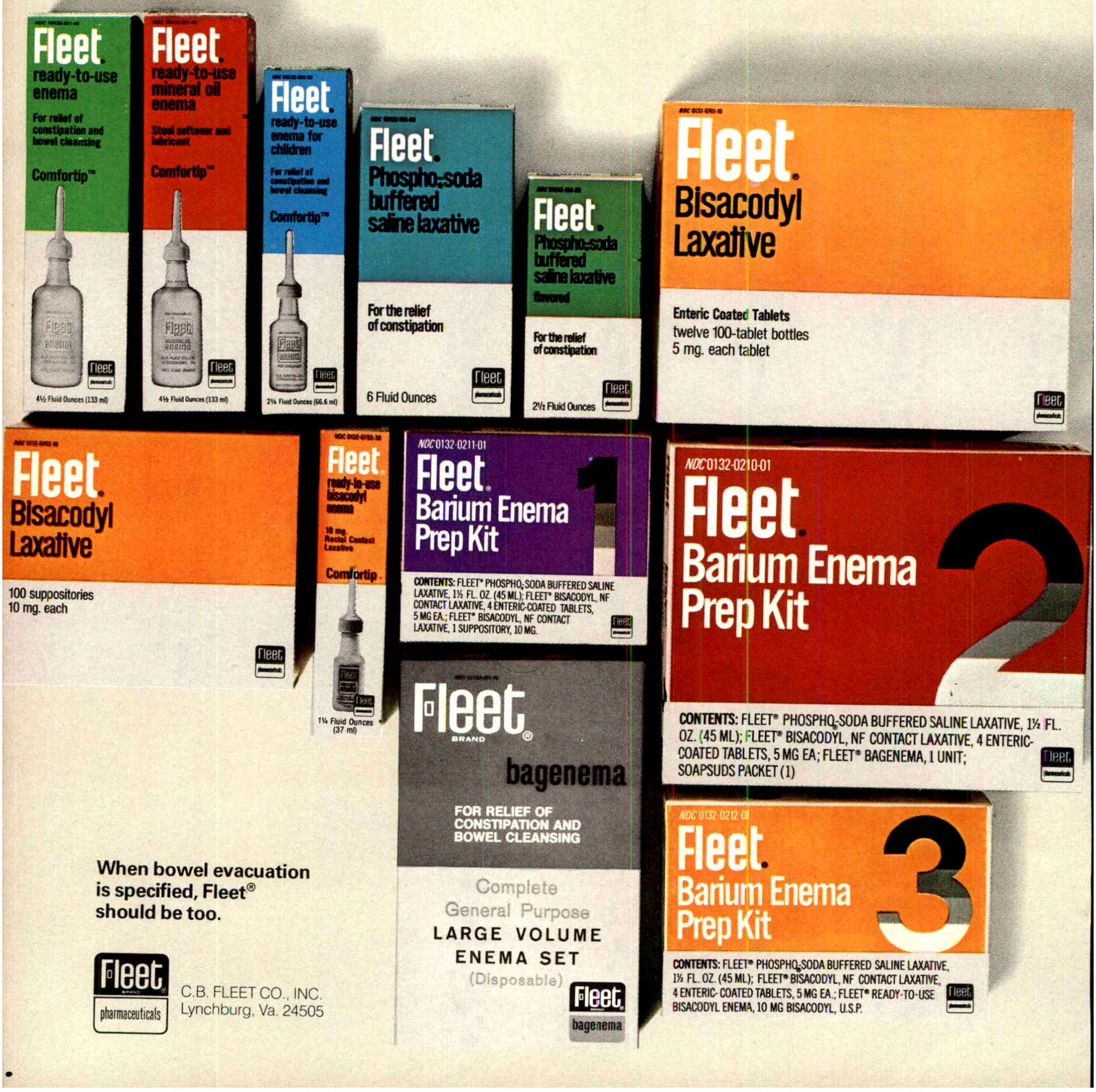
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VOLUME 71 MAY, 1979 NUMBER 5

# Low Incidence of Bacteremia Following Endoscopic Retrograde Cholangiopancreatography (ERCP)

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Wichita Falls, TX
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Valhalla, NY

Fifty patients (29 females) undergoing ERCP were studied prospectively for the occurrence of bacteremia associated with this endoscopic procedure. Each patient had blood samples drawn for aerobic and anaerobic cultures before endoscopy, after entering the duodenum, 5 and 15 minutes after cannulation of the papilla of Vater. Subcultures were made at 24 and 48 hours for a total of 1,200 cultures. No positive cultures were obtained in 48 patients. One patient developed a *Staphylococcus epidermidis* bacteremia during the procedure. The cleansing technic for the instruments consisted of alcohol and water only. Prophylactic antibiotics were not administered. In contrast to other gastrointestinal procedures, our results suggest that bacteremia is an uncommon occurrence in ERCP despite the longer duration of the procedure and instrumentation of a sterile duct system.

## INTRODUCTION

Bacteremia is known to follow a variety of gastrointestinal procedures, including esophageal dilatation,[1] upper gastrointestinal endoscopy,[2, 3] sigmoidoscopy,[4-6] colonoscopy[7,8] and barium enema.[9]

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From the Sarah C. Upham Section of Gastroenterology, New York Medical College, Westchester County Medical Center.
* Section of Infectious Diseases, New York Medical College, Westchester County Medical Center.

Although such bacteremias are generally transient, even a remote risk of endocarditis may warrant antibiotic prophylaxis for patients with prosthetic heart valves or other cardiac conditions.[10]

Endoscopic retrograde cholangiopancreatography (ERCP), which requires cannulation of the papilla of Vater, may be associated with increased trauma or abrasion of the mucosa. Furthermore, during the procedure, a cannula is passed through the endoscope which is clean but not sterile and thence into a sterile duct system. These increased risk factors have prompted us to study the incidence of associated bacteremia in this patient population.

## MATERIALS AND METHODS

We studied 50 patients (29 females, age range 29-77) who underwent ERCP for standard diagnostic indications. The pre-endoscopic diagnoses of the patients included 23 cases of chronic relapsing pancreatitis, 14 cases with obstructive jaundice, nine cases presenting with chronic epigastric pain of undetermined etiolgy and four cases with recurrent right upper quadrant pain after cholecystectomy and inconclusive intravenous cholangiography. Informed consent was obtained from each patient prior to the study.

All patients were afebrile, not receiving antibiotics and were without clinical evidence of existing pancreatobiliary or systemic infection.

Following premedication with diazepam 10 mg. given orally, propantheline bromide 15 mg. and atropine 0.4 mg. given subcutaneously, diazepam 10 mg. was administered intravenously. The throat was sprayed with Cetacaine® prior to introduction of an Olympus model JF-B gastroduodenoscope, which had been previously cleansed vigorously with a mixture of equal parts of 70% alcohol and water over the exterior surfaces for 1 minute and aspirated through the suction channel for 3-5 minutes. The suction part of the instrument was dismantled at intervals and cleansed with alcohol. Visible debris was carefully removed from the tip. Glucagon, 1 mg., was administered intravenously after the endoscope entered the duodenum to decrease the motility of the duodenum. The papilla was identified and cannulated. Meglumine diatrizoate 60% contrast material was then injected through the cannula, which had been previously cleansed vigorously with tap water only, to achieve visualization of the pancreatobiliary systems. No antibiotics were administered at any time during the study. The usual duration of the procedure was 45 minutes, which included endoscopy, radiography and performance of the venipuncture.

In 35 patients both the pancreatic and biliary systems were demonstrated. Visualization of the pancreatic duct alone was obtained in nine. In four patients there was visualization of the biliary tract alone, while there was complete failure in two others.

## CULTURES

Prior to endoscopy, a 19 gauge scalp vein needle was secured in an antecubital vein site which had been prepared with povidone-iodine and 70% alcohol. Ten milliliters of blood were drawn into a sterile disposable syringe before endoscopy, immediately following entry into the duodenum, five minutes after cannulation of the papilla of Vater and 15 minutes after completion of the cannulation. In two patients in whom the duct systems failed to opacify, cannulation was achieved and the same protocol for collection of samples was followed. The scalp vein needle was flushed with 0.5 ml. of heparin following all but the last sample.

Each blood sample was inoculated into trypticase soy broth and thioglycolate broth, 45 ml./bottle, (Becton, Dickinson and Co. Rutherford, NJ) and incubated at 37° C. The media contained STS with $CO_2$ added and the aerobic bottles were vented before incubation. All bottles were subcultured at 24 and 48 hours with a total of 1,200 cultures performed. Subculture and identification of organisms were performed using standard technics.[11] The aerobic subcultures were plated on blood and chocolate agar. The anaerobic subcultures were plated on blood agar and incubated with a catalyst generated $CO_2$ and $H_2$ jar (Gaspac®, BBL). All cultures were observed for growth for a minimum of 10 days following the last subculture before discarding.

## RESULTS

In 48 of the 50 patients, there were no positive cultures in samples obtained before, during or after ERCP which could be attributed to the procedure.

One patient, a 45-year old male with choledocholithiasis, developed *Staphylococcus epidermidis* bacteremia in the culture which was taken immediately after the endoscope entered the duodenum as well as in the 5- and 15-minute blood cultures obtained after cannulation. There were no clinical manifestations of the bacteremia and no treatment was necessary. An additional patient was found to have *Peptostreptococcus* bacteremia before endoscopy as well as in the samples obtained during the procedure but was totally asymptomatic.

## COMMENT

Despite reports of bacteremia in 8-12.5% of the patients undergoing esophagogastroscopy,[2, 3] we can attribute bacteremia to the procedure in only a single patient. In our patients there was the additional procedure of cannulation of the papilla of Vater and we had anticipated an increased incidence of bacteremia based on: 1. the increased time and associated trauma involved and 2. cannulation of patients in whom subclinical biliary infection might be present.

Bacteremia might be expected in sigmoidoscopy[4-6] because of the increased likelihood of fecal contamination in incompletely prepared patients. This, however, should not be anticipated in colonoscopy[7, 8] or barium enema[9] when a more careful bowel preparation is carried out reducing the fecal material and associated bacteria.

If lumenal bacterial flora play a role in those clinical situations associated with stasis and bacterial overgrowth, manipulations such as esophageal dilatation[1] or upper gastrointestinal endoscopy[2, 3] should be expected to result in bacteremia.

Oral hygiene seems likely to be related to this bacteremia. Trauma to the bacteria-rich oropharynx during instrumentation would account for an important source of entry of bacteria into the bloodstream. The type of instrumentation may also contribute to this increased risk. The duodenoscope used for ERCP is smaller in diameter than the diagnostic upper endoscope and has a smooth, rounded tip because of its lateral viewing configuration. It is easier to pass than the cconventional forward viewing instrument and thus is less traumatic. As our patient characteristics appear to be no different from those in previously reported series, the type of instrument and the care in passage may play a major role in the decreased incidence of bacteremia.

We are encouraged by the negative results in this study. Our technic of cleansing the instruments with alcohol and water mixtures appears to be sufficient to prevent bacterial complications at endoscopy. Other authors have advocated cleansing the instruments with glutaraldehyde or gas sterilizing the instruments.[12] Our, results, however, do not justify an extended disinfectant technic. Our data suggest that the sterility of the instrument as an exogenous source of contamination and subsequent bacteremia is less significant than an endogenous source of bacteremia. Transmission of other diseases, viral or bacterial, has never been reported as a complication of endoscopy indicating that fastidious cleansing technics are sufficient.

Incorporation of antibiotics with contrast material for injection through the cannula has been suggested by some authors.[13, 14] No proof of efficacy has been offered and it may introduce another source of risk.

Prophylactic use of antibiotics has been recommended in patients with obstruction of either the biliary or pancreatic duct systems[14] especially when obstruction is confirmed by injection of contrast material at ERCP. Prophylactic antibiotics were not used in the patients studied but we concur in its use in patients with suspected or demonstrated obstruction of either duct.

Despite the low incidence of bacteremia demonstrated in this study, special consideration should be given to patients with valvular heart disease to include prophylactic antibiotics and further studies addressing this potential hazard are awaited.

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*Valhalla, NY 10595*

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Vol. 71, No. 5
*Printed in the U.S.A.*

***Communication from Abroad***

# Definitive Diagnosis of Pancreatic Carcinoma with Percutaneous Fine Needle Aspiration Biopsy Under Ultrasonic Guidance

KOUICHI ITOH, M.D.*
TAKEO YAMANAKA, M.D.†
KOGORO KASAHARA, M.D.‡
MORIO KOIKE, M.D.**
AKINOBU NAKAMURA, M.D.*
AKINORI HAYASKI, M.D.*
KEN KIMURA, M.D.†
YASUHIKO MORIOKA, M.D.‡
and
TADASHI KAWAI, M.D.*
Minamikawachi, Japan

Definitive diagnosis of pancreatic cancer presents difficulties in that positive identification is often possible only by intraoperative biopsy. Recently, ultrasonic visualization of the pancreas has made preoperative diagnosis possible by furnishing a guide to percutaneous biopsy via a flexible 23-gauge, 0.6 mm. needle.

Ten patients with pancreatic carcinoma were biopsied with a fine needle under the ultrasonic image. Malignant cells were detected in eight cases. In two cases, however, hypocellularity of the specimen lead to a false negative result. No complication was encountered in this series. The procedure should be used as a primary tool in the diagnosis of pancreatic carcinoma.

Carcinoma of the pancreas is ranked as fifth in mortality of cancer deaths in Japan. Unfortunately clinical symptoms or signs, if any, are minimal in the early stage of this disease. A definitive diagnosis of pancreatic carcinoma can be made by biopsy during exploratory laparotomy but, in most cases, it is too late for effective medical care. We have employed aspiration biopsy under ultransonic image for one year to evaluate its feasibility for the detection of pancreatic malignancies.

## Materials and Methods

Ten patients with pancreatic carcinoma, two female and eight male, ranging from 46-67 yrs. of age, had percutaneous aspiration biopsy of the pancreas. Two patients with chronic pancreatitis, clinically diagnosed, were biopsied by similar technic.

The patients in this study were selected on the basis of demonstration of mass in the pancreas by the echogram.

---

* Department of Clinical Pathology, Jichi Medical School.

† Department of Internal Medicine, Jichi Medical School.

‡ Department of Surgery, Jichi Medical School.

** Department of Pathology, Jichi Medical School.

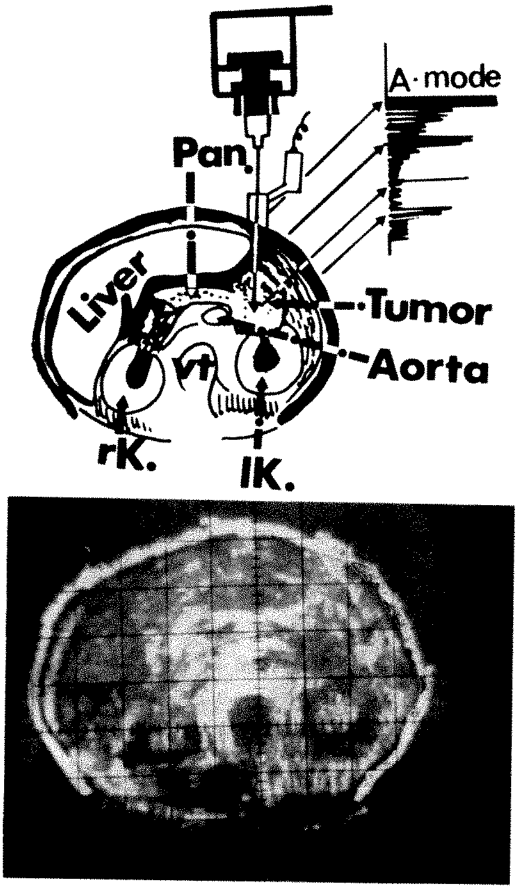

Fig. 1—A schematic (top) and corresponding ultrasonic picture (bottom) on a cross-section plane at the level of the kidneys. It demonstrates a mass in the tail of the pancreas. The schema shows a pathway of the needle into the pancreatic tumor with an aspiration pilot transducer. Pan, pancreas; rK, right kidney; lK, left kidney; vt, vertebral body.

Compound contact B-scanning ultrasound examinations were carried out with a Model Aloka SSD60-B and a scan converter image memory system Model XA-21. A special pilot transducer, 2.25 MHz, 10 mm. in diameter, nonfocused, has a central cannula (2 mm. in diameter) through which a fine needle is introduced. The skin in the region is sterilized and a local anesthetic is injected. A 23-gauge needle, 0.6 mm. in diameter and 20 cm. in length, attached to a disposable 10 ml. syringe with an aspiration piston was inserted percutaneously into the tumor mass of the pancreas under the B-scanning image which was visualized on the oscilloscope. A-mode display was used (Fig. 1). The whole needle itself is not visualized ultrasonically but the tip of the needle could be visualized on A-mode. The echo of a needle tip is the scattered wave at the point of the discontinuity between the fine needle and the pancreas. We could visualize the needle tip on the A-mode scan during the aspiration of a solid tumor mass because of poor echo of the pancreatic carcinoma.

The fine needle may pass through the gastrointestinal tract and/or the liver. Before the puncture, the distance from the skin to the puncture target plus the length of the pilot transducer was marked on the needle using a needle stop. The syringe and piston was withdrawn under forcible negative pressure and the specimen ejected onto the glass slides. Some thin smears were made, immediately fixed in 95% ethanol and then prepared with Papanicolaou stain, periodic acid Schiff stain, hematoxylin and eosin stain and Giemsa stain. Aspiration was repeated twice on each patient. After biopsy, patients were kept on bed rest for 24 hours.

## RESULTS

Ten aspiration biopsy specimens of the pancreas were obtained; eight of them showed satisfactory cellularity. Cytological diagnosis of the adenocarcinoma was made in these cases; seven cases of Class-V, and one case of Class-IV (Table I and Figs, 2a and 2b). In two cases, however, malignant cells could not be found because of insufficient sampling and the cells were classified as Class-I. In addition, the two patients with chronic pancreatitis yielded smears showing no malignant cells but rather many normal cells of the pancreas.

TABLE I

ASPIRATION BIOPSY UNDER ULTRASONIC GUIDANCE

| Case no. | Age | Sex | Ultrasound findings, size of mass on echogram | Cytological findings | Complication | Final diagnosis |
|---|---|---|---|---|---|---|
| Case 1, S. S. | 65 | M | Mass in tail of pancreas<br>5 × 4 cm. | Class-V | (−) | Adenocarcinoma in tail of pancreas[*]<br>(aspiration biopsy) |
| Case 2, H. O. | 62 | F | Mass in head of pancreas<br>4 × 2.5 cm. | Class-IV | (−) | Adenocarcinoma in head of pancreas<br>(exploratory laparotomy) |
| Case 3, T. U. | 63 | M | Mass in head of pancreas and enlarged gallbladder<br>3.5 × 3 cm. | Class-V | (−) | Adenocarcinoma in head of pancreas with metastasis to liver<br>(exploratory laparotomy) |
| Case 4, S. H. | 65 | M | Mass in corpus of pancreas<br>4 × 3 cm. | Class-V | (−) | Adenocarcinoma in corpus of pancreas<br>(laparoscopy) |
| Case 5, S. T. | 51 | M | Mass in head of pancreas<br>8 × 4 cm. | Class-V | (−) | Adenocarcinoma in head of pancreas<br>(exploratory laparotomy) |
| Case 6, I. T. | 46 | M | Mass in head of pancreas and dilatation of bile duct<br>4 × 2.5 cm. | Class-I | (−) | Adenocarcinoma in head of pancreas<br>(exploratory laparotomy) |
| Case 7, T. S. | 64 | M | Mass in head of pancreas<br>5 × 3 cm. | Class-V | (−) | Adenocarcinoma in head of pancreas<br>(laparoscopy) |
| Case 8, K. S. | 64 | M | Mass in tail of pancreas with metastasis to liver<br>3 × 2.5 cm. | Class-V | (−) | Adenocarcinoma in tail of pancreas and metastasis to liver<br>(laparoscopy) |
| Case 9, S. M. | 52 | M | Mass in head of pancreas<br>6 × 4 cm. | Class-V | (−) | Adenocarcinoma in head of pancreas[*]<br>(aspiration biopsy) |
| Case 10, M. I. | 67 | F | Mass in head of pancreas<br>5 × 3 cm. | Class-I | (−) | Adenocarcinoma in head of pancreas[*]<br>(cytology of bile: Class-V) |

[*] with pancreatic angiography and percutaneous transhepatic cholangiography.

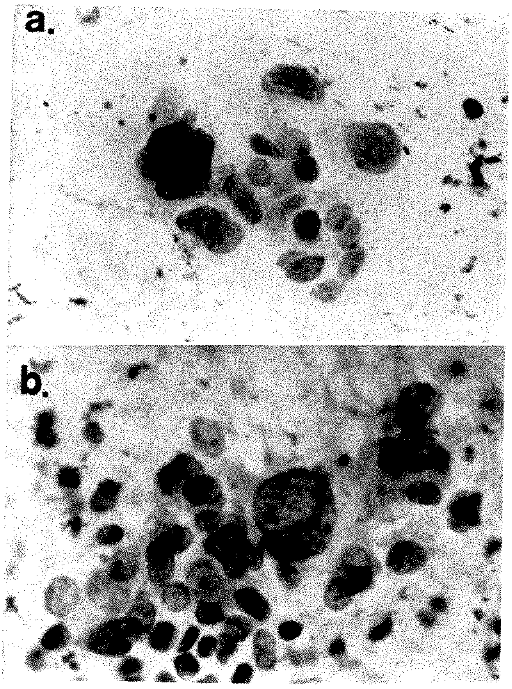

Fig. 2—Malignant pancreatic tumor cells aspirated from *a*: Case 1 and *b*: Case 2 (Papanicolaou stain, original magnification x400).

## COMMENT

Hancke, in 1975, was the first to perform needle aspiration biopsy of the pancreas. He employed a fine needle with an outer diameter of 0.6 mm. attached to a syringe and piston. The percutaneous aspiration was performed through the liver and/or the stomach.[1] Additional experience with the procedure was reported by Smith.[2]

While sonography has enabled identification of pancreatic masses as small as 3-4 cm. in diameter, the technic does not differentiate between benign and malignant tumors. Our experience with sonography-guided percutaneous needle biopsy has indicated that this procedure permits histologic diagnosis. Although the series is small, the biopsies were positive in eight of 10 cancers (80%), unsatisfactory in two patients and correctly negative in two of two patients with chronic pancreatitis. There were no false positive findings. These results are similar to those reported by Hancke and Smith.

Only abnormal bleeding tendency was a contraindication for percutaneous biopsy. No complications were encountered despite the possibilities of hemorrhage, pancreatic fistula and/or pancreatitis as judged by serum amylase elevation. On the other hand, Burg, using Silverman and Menghini needles and wedge resections, reported a 3.2% complication with six deaths for 742 patients; no complication was reported from the world literature by this author among the 34 cases in which fine needle aspiration was used.[4]

Four patients in our series had an exploratory laparotomy immediately after percutaneous needle pancreatic biopsy. The puncture site could not be identified grossly. We believe, therefore, that fine needle aspiration of the pancreas under ultrasonic image is a rapid, safe and accurate procedure. It can be utilized without fear of complication as a bedside laboratory procedure and should be used as a primary tool in the diagnosis of pancreatic carcinoma. The aspiration biopsy may be performed by using the multielement transducer[5] with a central cannula or connected adaptor for percutaneous punctures.

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# Dilemma of Pancreatic Ductal Carcinoma*

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The tragic fact is that the incidence of ductal carcinoma of the pancreas is clearly rising and the mortality rate remains unchanged.[1, 2] The low survival rate means that incidence and mortality rates are almost identical. For the patient and clinician this current outlook is bleak for an important disease, which has risen from an incidence of 2.9-9.0 per 100,000 from 1920-1970, an increment of over 300% and whose incidence continues to rise at approximately 15% per decade.[3, 4] It is now among the leading causes of cancer death, being second only to colorectal carcinoma among gastrointestinal maliginancies.[4]

Today cure depends upon surgery. Despite improvements that have lowered the surgical mortality of resection long-term survival remains unchanged. In searching for means of improving survival, attention has been focused on achieving earlier diagnosis in this retroperitoneal organ that is relatively inacessable. Whether earlier diagnosis will increase long-term survival remains to be determined. This hope, however, has led to the development of a large and sometimes bewildering, panoply of diagnostic tests. The precise value, role and sequence of such tests remains to be established. Even if the new diagnostic technics do not improve long-term survival, they may accelerate diagnosis, shortening the period of uncertainty and hospitalization, a benefit not to be lightly dismissed. Although diagnosis earlier in its natural history will probably result in a longer survival time from discovery to death, this is of no real significance. Its potential importance lies in whether earlier diagnosis will lead to improved resectability and whether this in turn will lead to an increase in long-term survival. Until the answers are obtained, we are faced with the continuing dilemma of how to proceed.

In order to determine how clinicians cope with the problem of pancreatic carcinoma and in an attempt to determine the value of various procedures both in establishing the diagnosis and effecting cure, we thought it worthwhile to review our experiences with this disease.

## METHODS AND RESULTS

During the ten-year period, 1965-1974, 360 cases of carcinoma of the pancreas, either clinically or histologically established, were treated at the Beth Israel Medical Center, a major metropolitan community hospital with a medical school affiliation. These cases represented 0.20% of the admissions to the Medical Center. In an effort to evaluate our attempts at earlier diagnosis, the last 100 cases during the study period were analyzed. These cases were all encountered between the years 1972-1976.

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### CLINICAL FEATURES

Clinical symptoms occurred, on the average, three months prior to admission to the hospital. The predominant historical features were weight loss (36%), abdominal pain (32%), jaundice (25%), anorexia (32%) and nausea (26%). Back pain phlebitis and pruritus were relatively rare, seen in less than 2% of patients.

Abnormal physical findings were encountered in almost all patients. Jaundice (58%), abdominal mass (24%) and hepatomegaly (40%) were common. Palpable gallbladder (7%) and splenomegaly (1%) were rare.

Significant and most common laboratory abnormalities were SGOT (83%), glucose (40%), bilirubin (40%), alkaline phosphatase (42%), stool guaiac (64%), serum amylase (35%).

### PROCEDURES

Gastrointestinal series was positive in only one of 12 performed; angiography in five of eight; endoscopic retrograde cholangiopancreatography (ERCP) in six of seven; liver scan for metastasis in 11/12; liver biopsy in 6/6; laparoscopy in 4/4; percutaneous transhepatic cholangiogram (PTC) in 5/5; gallbladder series in 4/9 and intravenous cholangiogram in 1/3. Sonography and computerized axial tomography scan were not available.

The difference in the approach to diagnosis used by internists and surgeons was dramatic. Internists generally ordered many tests, in order to establish the diagnosis. Surgeons generally performed few tests before proceeding to laparotomy.

### SURGERY AND SURVIVAL

Nineteen patients had surgery at which time the diagnosis was either established or confirmed. None were considered resectable. No patient in the entire series lived more than 18 months and the average survival was six months from the time of diagnosis. The average time from onset of symptoms to death was 21 months even though most patients in the series had a diagnostic work-up started within three months of their first symptom. Despite the relatively rapid evaluation of many of these patients the two-year survival rate was zero.

### COMMENT

Several things became apparent as we reviewed our experience. Although internists performed many tests and surgeons proceeded to laparotomy much earlier, there were no long-term survivors, or any patients considered suitable for pancreatic resection in this group, although pancreatectomy is performed at our institution for this disease. The diagnosis was ultimately made by both approaches. These dismal results were obtained despite the fact that many patients presented themselves within three months of the onset of symptoms.

Many of the patients in the series already had metastases when first admitted, and it would be anticipated that their life expectancy would be short. There were others, however, who when explored showed no obvious metastases but were not considered candidates for radical resection for other reasons. This group which was only surgically palliated, also developed spread and died within a very short time. This apparent postsurgical acceleration

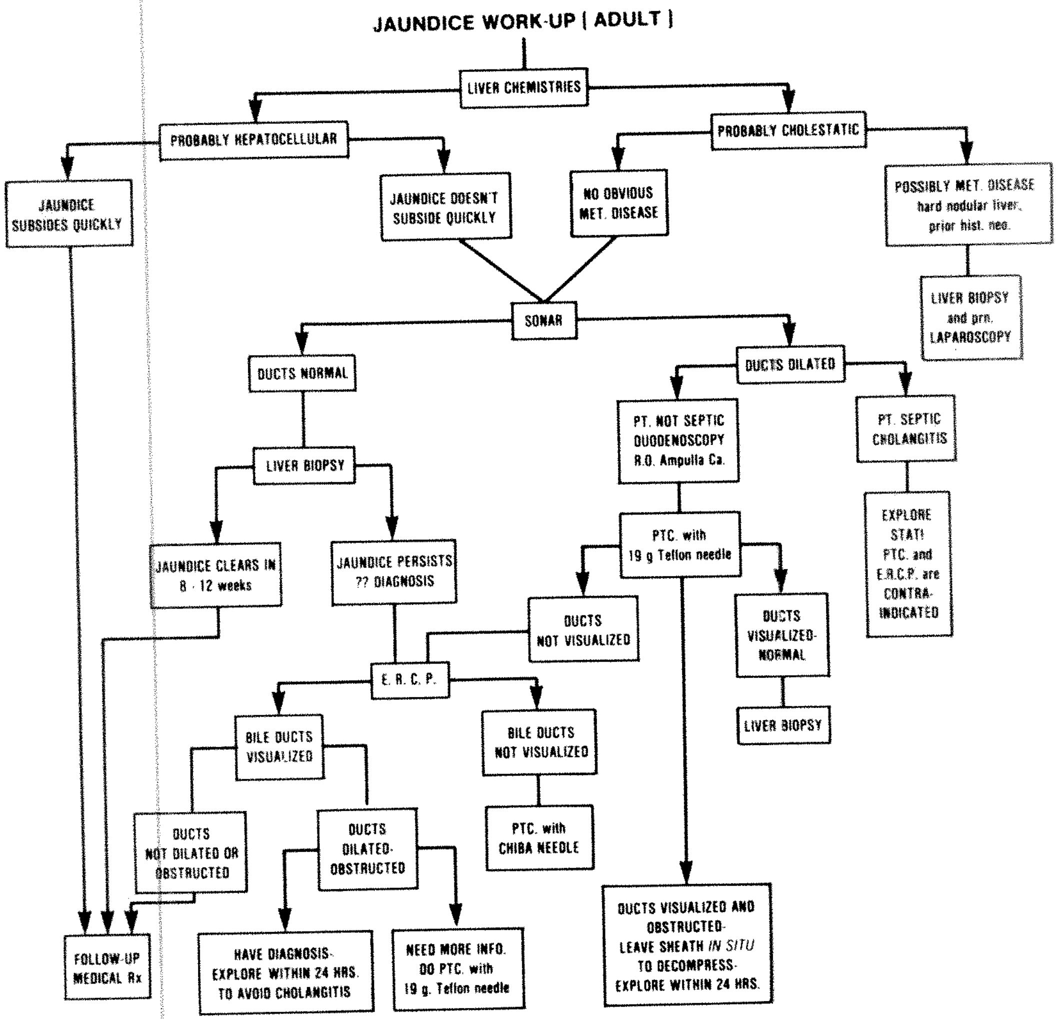
JAUNDICE WORK-UP (ADULT)
LIVER CHEMISTRIES
PROBABLY HEPATOCELLULAR
PROBABLY CHOLESTATIC
JAUNDICE SUBSIDES QUICKLY
JAUNDICE DOESN'T SUBSIDE QUICKLY
NO OBVIOUS MET. DISEASE
POSSIBLY MET. DISEASE hard nodular liver, prior hist. neo.
LIVER BIOPSY and prn. LAPAROSCOPY
SONAR
DUCTS NORMAL
DUCTS DILATED
PT. NOT SEPTIC DUODENOSCOPY R.O. Ampulla Ca.
PT. SEPTIC CHOLANGITIS
LIVER BIOPSY
EXPLORE STAT! PTC. and E.R.C.P. are CONTRA-INDICATED
PTC. with 19 g Teflon needle
JAUNDICE CLEARS IN 8 - 12 weeks
JAUNDICE PERSISTS ?? DIAGNOSIS
DUCTS NOT VISUALIZED
DUCTS VISUALIZED-NORMAL
E. R. C. P.
LIVER BIOPSY
BILE DUCTS VISUALIZED
BILE DUCTS NOT VISUALIZED
DUCTS NOT DILATED OR OBSTRUCTED
DUCTS DILATED-OBSTRUCTED
PTC. with CHIBA NEEDLE
DUCTS VISUALIZED AND OBSTRUCTED-LEAVE SHEATH *IN SITU* TO DECOMPRESS-EXPLORE WITHIN 24 HRS.
FOLLOW-UP MEDICAL Rx
HAVE DIAGNOSIS-EXPLORE WITHIN 24 HRS. TO AVOID CHOLANGITIS
NEED MORE INFO. DO PTC. with 19 g. Teflon needle

Fig. 1—Algorithm for the diagnosis of jaundice in adults.

could be due either to the abundant vascularity and lymphatic drainage to the pancreas alone, or related to microembolic spread incident to the surgical manipulation.

If micro-metastases already exist at the time of surgery, earlier diagnosis leading to exploration before such metastasis occurs will improve the dismal results. Should it be true that surgery accelerates spread, then other approaches, such as preoperative radiation or chemotherapy may have value.

The lack of pancreatic resections in this series is of interest. Whether surgeons avoided resection because of the high operative mortality and/or the low yield in terms of survival, is not clear.

Since many patients with pancreatic carcinoma present with jaundice, there have been several attempts to develop algorithms for guidance.[5, 6] Computer programs have been attempted.[7] To guide our staff, we developed an algorithm based on the swing points of liver "function" tests and sonography (Fig. 1). Another approach which has value in early diagnosis is cytology obtained at ERCP.[8] Percutaneous aspiration cytology is helpful in establishing a tissue diagnosis in unresectable cases.[9] Pancreatic secretory tests are useful in some centers.[10]

For want of better direction, research thrust continues to look to achieve better survival via earlier diagnosis. That this will occur is not at all sure. Other approaches include identifying risk factors and investigating high risk populations more aggressively.[11] These risk factors include race, diabetes, cigarette smoking, gallstones and cholecystectomy. The value of sonography, computerized axial tomography, radionuclide scanning with new isotopes and superselective angiography with image magnification is not yet established but appears promising.[12-14] Although their use may result in earlier diagnosis, it is not at all sure that this will increase survival. One study already suggests scanning does not improve survival.[15] Enzymatic and immunologic tests are not yet practical.[14, 16, 17] Until it is known whether earlier diagnosis will result in improved survival, the dilemma as to future investigative pathways will continue to exist.

## ACKNOWLEDGMENT

Our thanks to Frank Chateau, P.A. for his help in this work.

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# Hemorrhage Due to Retrograde Prolapse of Stomach

## AN ENDOSCOPIC DIAGNOSIS

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A case of recurrent hemorrhage due to localized gastric mucosal congestion from retrograde prolapse during severe retching is described. Historically, this condition may mimic the "Mallory-Weiss syndrome" and endoscopically, this lesion may be mistaken for "gastritis". This rarely recognized condition may be an explanation for some cases of cryptic hematemesis.

Upper gastrointestinal hemorrhage may be caused by a variety of acute and chronic lesions. Over a decade of experience with early endoscopic examination in an urban population consuming above average amounts of alcohol has revealed that acute mucosal lesions are a major cause for the bleeding. Those observed included gastritis and gastric erosions, duodenitis and duodenal erosions, acute ulcers and mucosal tears of the Mallory-Weiss type.[1]

The continued use of fiberoptic endoscopy made us recognize recently an unusual cause for mucosal bleeding from the stomach, in an alcoholic patient who had experienced over 50 separate episodes of hematemesis. The bleeding seemed to occur from congestion of an area of the gastric mucosa which repeatedly prolapsed into the esophagus during severe retching.[2-4]

## CASE REPORT

A 52-year old white male was admitted in December, 1976, with vomiting of bright blood following severe retching after a seven-day spree of drinking alcohol.

Physical examination revealed an obese, intoxicated, uncooperative man. His blood pressure was 140/80; pulse rate, 100/min.; respirations, 20/min. and temperature, 37.5°C. Testicular atrophy, gynocomastia and ascites were present.

Laboratory data: Hct., 33.2%; WBC, 14,600/cu.mm. with a shift to the left. His coagulation screen, including a platelet count, prothrombin time and partial thromboplastin time, was normal. Liver tests, except for a slightly elevated alkaline phosphatase of 124 I.U./l. serum amylase, were normal.

After admission, he continued to retch and vomit bright blood. His hematocrit fell to 22.5% and he was given blood transfusions.

Endoscopic examination was performed with a fiberoptic panendoscope after giving topical anesthesia to the pharynx. With the instrument in the mid esophagus, the lower esophageal mucosa was observed to be inflamed with a few erosions but not actively bleeding. Through

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From the Section of Gastroenterology, New York Medical College/Westchester County Medical Center.

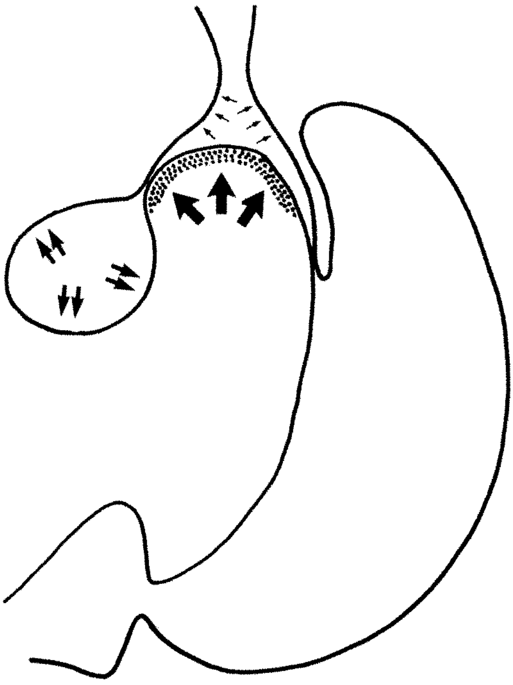

Fig. 1—Forceful prolapse of the lesser curve region of the stomach (thick arrows) stretches the lower esophageal sphincter (small arrows), resulting in a disc-shaped bleeding lesion (shaded area) and aggravation of the already existing esophagitis by producing congestion, friability, or a tear (small arrows). Severe stretching due to compression in the adjacent area (double arrows) probably can produce mucosal tears resembling a Mallory-Weiss lesion.

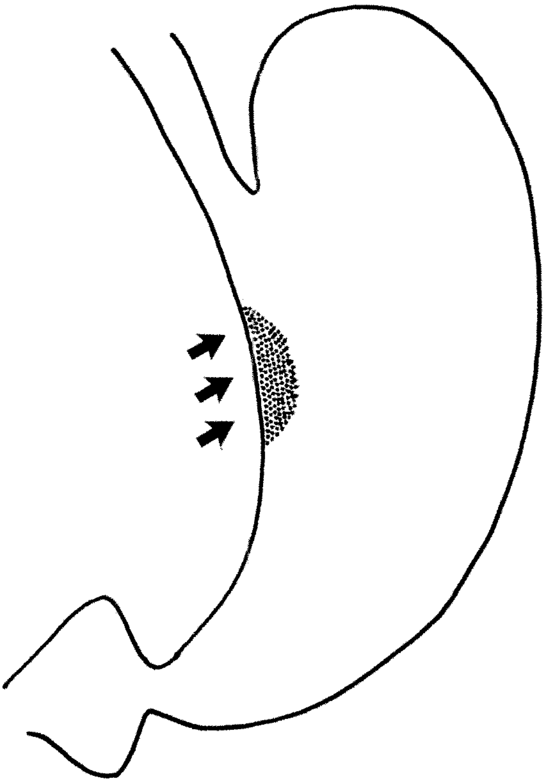

Fig. 2—Recently prolapsed area on the lesser curve (shaded area) appears congested, friable and bleeding and has a disc-like shape.

a patulous sphincter a small sliding hiatus hernia was seen. At this time the patient started to retch repeatedly. This resulted in prolapse of the stomach through the patulous sphincter for several centimeters into the lower third of the esophagus (Fig. 1). The prolapsed mucosa at first appeared almost normal but with repeated severe prolapse it became congested and started oozing bright blood. The sphincter region which was already inflamed and friable, was acutely stretched by the prolapsing stomach and also started actively bleeding. The examination was completed after giving additional intravenous diazepam. On inspecting the stomach the area which had prolapsed was noted to be the posterior lesser curvature region which appeared friable and actively bleeding over a disc-shaped area measuring over 5 cm. in diameter.

The patient was managed conservatively. He underwent a barium study which confirmed the presence of a sliding hiatus hernia with free reflux.

In the past he admitted to having experienced over 50 separate episodes of bright red hematemesis associated with alcoholic sprees. The four previous admissions to this center, from August, 1972 to the present when he underwent endoscopic examinations, showed moderate to severe esophagitis and a congested stomach mucosa interpreted as "gastritis".

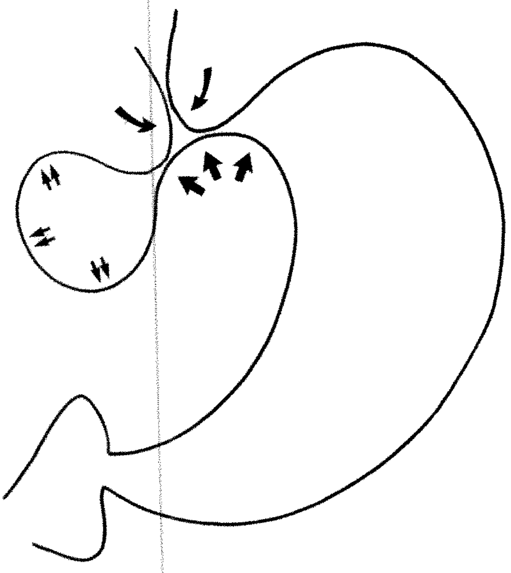

Fig. 3—Forceful retroperistalsis against a closed sphincter. The area of the stomach distal to the cardioesophageal junction may be acutely stretched (double arrows) resulting in a Mallory-Weiss type of tear (hypothetical).

## COMMENT

The diagnosis in this patient was made in a fortuitous manner. During endoscopic examination, when the tip of the instrument was in the mid esophagus, the patient started to retch repeatedly. Each time this occurred, the posterior lesser curvature aspect of the stomach was seen to forcibly prolapse several centimeters into the lower esophagus. This was noted to result in severe stretching of the lower esophageal sphincter region and progressive rapid congestion of the prolapsed gastric mucosa. Soon, bleeding was noted to occur from both areas, the already inflamed lower esophagus and a disc-like area on the lesser curvature of the stomach (Figs. 1 and 2). It would not have been possible to observe the occurrence of this interesting lesion if the retching had been abolished by heavier sedation during the procedure.

It is our belief that this phenomenon can explain the occurrence of congestion and tears at and on either side of the gastroesophageal junction in patients who retch severely. If the lower esophageal sphincter region is lax, the prolapsing stomach appears to acutely stretch it with resultant production of a lower esophageal tear. If it does not produce a tear, it may result in congestion and friability, aggravating an already existing peptic esophagitis as in our patient. Simultaneously, the prolapsing gastric mucosa becomes severely congested and friable over a disc-shaped area and starts bleeding (Fig. 2).

On the contrary, if the lower esophageal sphincter remains tight and prevents prolapse, sudden stretching and tearing of the stomach immediately distal to the cardioesophageal junction may occur. This may be indistinguishable from a Mallory-Weiss type of tear occurring in the stomach[5] (Fig. 3). Evidence for this lesion cannot be obtained by endoscopic examination because visualization distal to the closed cardioesophageal junction would not be possible.

Laforet,[4] after observing a similar lesion, surmised that the prolapse occurred because of over redundancy of the distal gastric mucosa relative to the firmly fixed mucosa of the inflamed lower esophagus. Our endoscopic impression, however, is that not only the mucosa but all layers of the stomach were involved in the prolapse, though this is difficult to prove. The basic abnormality is probably laxity of that portion of the stomach. In our patient it may be due to a redundant gastrohepatic ligament which is a remnant of the ventral mesentery which has failed to adequately regress. The lower esophageal sphincter tone probably merely determines the site of the possible tear.

Thus, the requirements for the production of this unusual and rarely recognized lesion are severe retching and forceful retrograde prolapse of the stomach.[2, 3] Treatment is probably conservative until further light is shed on the ligamentous anchors of the stomachs of these subjects. Manometric evaluation of sphincter competence and antireflux surgery, however, may be considered.

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# Brucella-induced Cholecystitis

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Acute cholecystitis is a rare complication of systemic brucellosis. This report details the occurrence of acute noncalculous cholecystitis in which *Brucella suis* was cultured from both the blood and the gallbladder. A discussion of the various diagnostic tests and the recommended therapy for brucellosis is included.

## INTRODUCTION

Brucellosis is a world wide zoonosis caused by gram-negative rods belonging to the genus *Brucella*. Acute cholecystitis is a rare complication of this disease. This report details the occurrence of acute noncalculous cholecystitis due to systemic brucellosis.

## CASE REPORT

A 34-year old white male microbiologist, of Eastern European extraction who had been living in the United States for two years, was admitted to the hospital with a five-day history of fever, headache and general malaise. He had previously been in good health. His work involved immunologic research with no exposure to live animals. He did handle tissue samples of malignant solid tumors. There was no ongoing research in his department with *Brucella* organisms.

On admission he appeared acutely ill. His temperature was 39.0° C; pulse, 110/min. There was no rash nor scleral icterus. Small, tender lymph nodes were palpable in the axilla and cervical chains. His neck was supple, chest clear and cardiac examination normal. The liver spanned 9 cm. and did not extend below the right costal margin. The spleen tip was palpated 1 cm. below the left costal margin. The bowel sounds were normal and the abdomen soft.

Initial laboratory data revealed a leucocyte count of 8,400/cu. mm. with 42 neutrophils; 40 lymphocytes; 14 monocytes and 4 eosinophils. Electrolytes, glucose, renal function and liver tests were normal. A mono-spot was negative. Erythrocyte sedimentation rate was 18 mm./hr. Antinuclear antibody and *L.E.* cell preparation were negative. Urine and stool cultures gave no growth. Cerebrospinal fluid was clear, colorless with no leucocytes and a negative gram stain and India ink preparation. Chest x-ray and electrocardiogram were normal.

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From the University of Miami School of Medicine, Department of Medicine, Division of Gastroenterology.

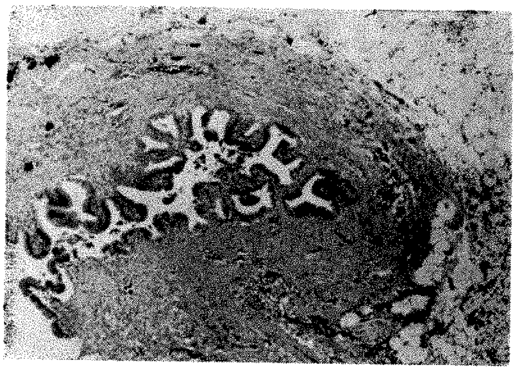

Fig. 1—Low power photomicrograph showing cholecystitis and inflammation on the serosal surface (Hematoxylin and eosin, original magnification x16).

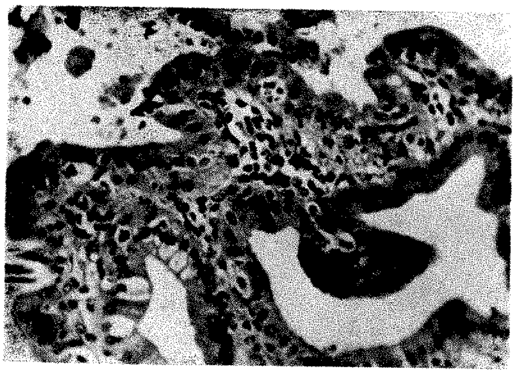

Fig. 2—High power photomicrograph showing prominent polymorphonuclear infiltrate and intraluminal debris (Hematoxylin and eosin, original magnification x100).

*Hospital course:*—On the second hospital day an I.V.P. was interpreted as normal. The patient's temperature was 39.7° C. He began to complain of right-sided abdominal pain with nausea. Examination revealed a tender right upper quadrant, localized under the right costal margin. A KUB was unremarkable and serum amylase was normal. An ultrasound was done which showed no stones in the gallbladder. A $^{99m}$Tc liver scan revealed no filling defects in the liver. Febrile agglutinins, drawn on the first hospital day, returned positive for *Brucella* at a 1:320 dilution. The febrile course persisted over the next three days while the abdominal pain waxed and waned. Blood cultures remained negative. On the sixth hospital day the patient began to vomit and examination of the abdomen revealed right upper quadrant guarding and rebound. A palpable, ill-defined mass, thought not to be the liver, was felt. A diagnosis of acute cholecystitis was made.

Febrile agglutinins were repeated on the same day and were positive for *Brucella* in a titer of 1:1280. The patient was started on streptomycin 1 gm. I.M. daily and tetracycline 2 gm. orally per day. The abdominal pain continued and a repeat ultrasound again failed to disclose stones but did show an enlarged gallbladder. On the seventh hospital day the patient had a right subcostal incision. There was an acutely inflamed gallbladder with a thin layer of exudate over the outside. The gallbladder was removed in its entirety. The common duct was not explored. The liver appeared normal. On opening the gallbladder, approximately 6-7 cc. of pus were expressed. No stones were found. Cultures of the pus, bile and scrapings of the gallbladder were taken. The pus eventually grew out *Brucella suis,* the other cultures remained negative.

Sections of the gallbladder (Figs. 1 and 2) revealed a fairly intact mucosa with edema and a polymorphonuclear infiltrate. Histologic diagnosis was acute cholecystitis. No granulomas were found. Postoperatively the patient did well. He was continued on streptomycin and tetracycline and became afebrile on the ninth hospital day. The patient was discharged on the 18th hospital day on oral tetracycline until a 21-day course was completed. Blood cultures, drawn on the first hospital day, were reported as positive for *Brucella suis* 26 days later. The patient remained well at home and was able to return to work six weeks after the onset of his illness.

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***Communication from Abroad***

# Neonatal Duodenal Obstruction

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The records of 40 infants with intrinsic duodenal obstruction have been reviewed. Of these more than half had no bile in the vomit. Persistent vomiting has been considered as the major factor of doubt regarding duodenal obstruction. The incidence of other associated congenital abnormalities was 70%. The over all mortality rate was 42.5%. The association of mongoloidism to the intrinsic duodenal obstruction was found approximately in every third infant. The low birth weight without other congenital abnormality has very little effect on the mortality rate.

The duodenal obstruction in a neonate was first reported by Calder in 1733.[1] It was not until 1905 that the first successful operation for its relief was performed by Vidal.[2] Benson,[3] during the period of the next 15 years, could find only 57 survivors; the number doubled between 1952 and 1960.

The duodenal obstruction may be either intrinsic due to atresia, diaphragm, stenosis, or extrinsic, due to incomplete rotation with associated adhesions or volvulus of the mid gut (Gross 1953).[4] Eighty-five neonates with duodenal obstruction were admitted to the Adelaide Childrens Hospital between 1963 and 1974. Forty of them were with intrinsic obstruction. This report analyzes these 40 cases for age and sex, birth weight, the clinical presentation, associated anomalies, type and site of lesion, results of surgery and mortality.

## OBSERVATIONS

*Age and sex:*—Age at the time of admission to the hospital varied from 1 day to 1 month but the majority came within the first three days (Table I). There were 22 females and 18 males in the series.

*Prematurity and birth weight:*—Information about the pregnancy was recorded in 31 instances. Eleven mothers had hydramnios. Fifteen neonates were premature and in three of them gestation was less than 36 weeks. Of these three, one was the second of triplets and two were from among twins. Thirteen of 40 cases were less than 2.5 kg. of weight and two 1.6 and 1.2 kg. at birth.

*Clinical features and associated anomalies:*—Thirty-eight of the cases were admitted with acute upper intestinal obstruction of which two had tracheoesophageal fistula with intrinsic duodenal obstruction. They were having clear vomit but their main symptoms were respiratory. One of these two had severe cardiac lesions and was moribund at admission.

The onset of symptoms was within three days of life in 31 cases, vomiting being the most prominent presenting symptom (Table II). Presence of bile in vomitus was recorded in 18 cases and five had dark blood in addition. Abdominal distention was seen in eight cases. Jaundice was pres-

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TABLE I

Age Distribution

| Age | No. of cases |
|---|---|
| 1-3 days | 31 |
| 4-7 days | 8 |
| 1 week-1 month | 1 |
| Total | 40 |

TABLE II

Clinical Presentation

| Symptoms | No. of cases |
|---|---|
| Vomiting | 38 |
| Bilious | 18 |
| Billious + blood | 5 |
| Nonbilious | 15 |
| Distention | 8 |
| Jaundice | 9 |

TABLE III

Associated Congenital Anomalies

| Anomalies | In mongoloids | In others | Total |
|---|---|---|---|
| TOF | 1 | 1 | 2 |
| CVS | 8 | 3 | 11 |
| Anorectal agenesis | – | 2 | 2 |
| Meckel's diverticulum | – | 1 | 1 |
| Fibrocystic disease | – | 1 | 1 |
| Annular pancreas | 2 | 5 | 7 |
| Malrotation | – | 4 | 4 |
|  | 11 | 17 | 28 |

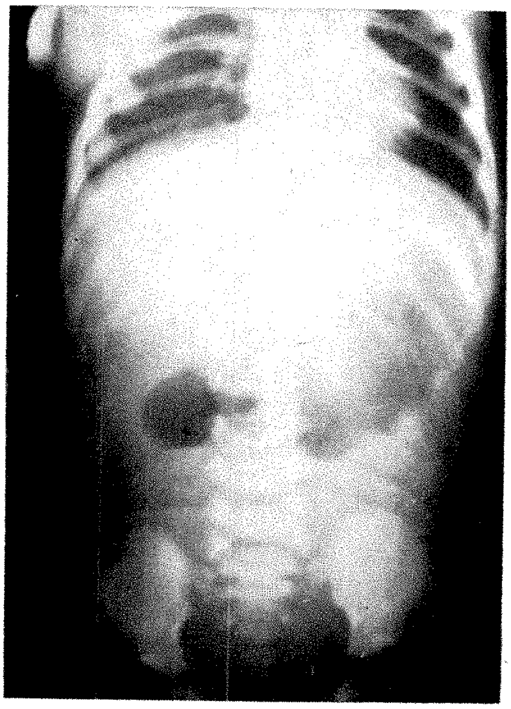

Fig. 1–Duodenal obstruction with typical double bubble appearance.

ent in nine patients. Exchange transfusion, because of increasing jaundice secondary to rhesus incompatibility, was needed in two while the remaining seven were presumed to have postnatal jaundice. Thirty five cases were dehydrated and seven were severely ill. Radiographic studies were carried out in all 40 cases of which 34 showed complete duodenal obstruction with typical double bubble appearance (Fig. 1). Five patients had gas in the stomach as well as in the small bowel on plain abdominal skiagram. In these doubtful cases barium meal study was helpful in reaching the diagnosis. Table III lists the associated anomalies. Seventy per cent of these neonates had one or the other abnormality, four had duodenal obstruction both due to intrinsic as well as extrinsic lesions. Sixteen were mongoloids (40%). Congenital heart disease was seen in all patients and annular pancreas in seven.

TABLE IV

TYPES OF INTRINSIC LESIONS

| Types of lesions | No. of cases |
|---|---|
| Atresia | 16 |
| Stenosis | 6 |
| Membrane or septum | 11 |
| Annular pancreas with stenosis or atresia | 7 |
| Total | 40 |

TABLE V

TYPES OF OPERATIONS IN 29 CASES

| Operations | No. of cases |
|---|---|
| Gastrojejunostomy | 2 |
| Duodenojejunostomy | 8 |
| Duodenoduodenostomy | 12 |
| Excision of membrane | 7 |
| Total | 29 |

*Type and site of lesion:*—These were determined by various investigations and operative findings. Atresia of the duodenum (16 cases) and membrane or septum (11 cases) formed the most common types of lesion (Table IV). The most common site of involvement was the second portion of the duodenum.

*Surgery and its results:*—Surgery was performed in 29 cases (Table V). Twenty of them had a transjejunostomy feeding tube beyond the anastomosis. Earlier duodenojejunostomy was a common operation but in later years duodenoduodenostomy was preferred. Eleven patients could not be operated upon for intrinsic duodenal obstruction. Five among the mongoloids and one from the others were considered unfit for surgery. Of the remaining five, three suffered from serious congenital heart disease besides being premature, one had severe pneumonia and one inhaled vomitus during transfer from another hospital and died soon after admission. All these 11 patients died. Twenty-three (80%) of 29 operated patients survived and were followed-up.

*Mortality:*—Mortality in the operated group was 20% whereas the over all mortality rate of neonates with intrinsic duodenal obstruction in the series was 41.5% (Table VI). The causes of death in the operated group are shown in Table VII.

## COMMENT

On reviewing the records we have found that 38 of 40 cases in the present series presented with acute upper intestinal obstruction. Of these 31 came within three days of life. There was no sex predilection. Information regarding the pregnancy was recorded in 31 instances and 11 (35%) of the mothers had hydramnios. Similar high incidence of association of hydramnios to upper gastrointestinal obstruction is reported by Lloyd and Clatworthy[5] in their series. The intrinsic duodenal obstruction is known for its association with low birth weight. Thirteen of 40 (32.5%) babies weighed less than 2.5 kg. More than half of the infants in the series did not vomit bile stained fluid while Schaffer[6] and Rickham[7] reported that vomitus almost always contains bile. This, in our cases possibly, is due to intrinsic lesion lying above the ampulla of Vater. The same findings were reported by Codres[8] and Young.[9] Thus the important point is that persistent vomiting in the neonate, whether the vomitus is bile stained or not should arouse the suspicion of duodenal obstruction.

High incidence of associated congenital abnormalities has been reported by several

TABLE VI

OVER ALL SURVIVAL AND MORTALITY

| Types of lesions | Cases | Number | Dead | Survivors |
|---|---|---|---|---|
| Atresia or stenosis | Mongoloids | 15 | 10 | 5 |
| With or without annular pancreas | Others | 14 | 6 | 8 |
| Membrane or septum | Mongoloids | 1 | 1 | — |
| | Others | 10 | — | 10 |
| Total | | 40 | 17<br>(41.5%) | 23<br>(57.5%) |

TABLE VII

CAUSES OF DEATH IN OPERATED GROUP

| Causes | No. of cases |
|---|---|
| Peritonitis | 3 |
| Bronchopneumonia | 2 |
| Renal failure | 1 |
| Total | 6 |

authors.[10, 11] In the present report the incidence was 70% and this is comparable to Young's observations.[9] Benson, et al[3] reported 31% incidence of mongoloidism while we had 16 (40%) mongoloids in our series indicating that approximately every third infant with intrinsic duodenal obstruction is mongoloid. Cardiovascular abnormalities were common and many of them were diagnosed at autopsy. Four neonates had both intrinsic and extrinsic duodenal obstruction. Annular pancreas was seen in only seven cases.

Surgery was performed in 29 cases of which 23 survived. The over all mortality rate in the present report was 42.5%, which is comparable to the reported rate of 33% by Low 1952 and better than the 60% of Benson, et al (1962).[3] The presence of severe congenital abnormalities was a more important contributory factor for over all mortality than was the low birth weight alone. When mongoloidism and intrinsic duodenal obstruction were combined, the operative mortality was lower than in others which tallies with the common clinical impression that mongoloid children withstand operative treatment better than the otherwise normal ones.

Duodenoduodenostomy was preferred to duodenojejunostomy although the latter procedure was done in most of the early cases. The transanastomotic tube was helpful in returning the aspirated fluid from the stomach and also for early feeding purposes but it is certainly not without hazards as dislodgement occurred on three occasions and jejunal perforation occurred twice. In more than half of our cases we used this tube.

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# Mechanism of Vasopressin Inhibition of Pancreatic Secretion

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## INTRODUCTION

It has repeatedly been demonstrated that the intravenous infusion of antidiuretic hormone (VP) to dogs significantly diminishes their exocrine pancreatic secretion responses to the administration of secretin.[1-6] Most investigators have attributed this inhibition in output to a direct effect of VP on the pancreatic ductal epithelium, in a fashion analogous to that on the tubules of the kidney.[1, 2, 4, 6] The possibility has been raised, however, that it is in fact the reduction in pancreatic blood flow, produced by the vasoconstricting action of VP, which accounts for its inhibition of pancreatic secretion.[3, 5]

In order to further elucidate the mechanism of inhibition of VP on the pancreas, we have investigated the effects of two synthetic analogues of the hormone on this organ. The first, 1-deamino-[8-D-arginine]-vasopressin (dDAVP), has potent antidiurectic activity but is a very weak vasoconstrictor. The second, N α-triglycyl-lysine-vasopressin (tGLVP), is enzymatically converted *in vivo* to lysine-vasopressin at a slow rate which decreases the significance of its antidiuretic action in relation to smooth muscle activities. It is hoped that such a relative separation of these two actions of VP would provide information as to which effect is responsible for exocrine pancreatic inhibition.

## MATERIALS AND METHODS

The pancreatic exocrine secretion of each of four adult female mongrel dogs was evaluated in response to dDAVP and tGLVP, using each animal as its own control. The dogs weighed 15-23 kg. and were maintained at a constant weight throughout the course of the study. They were fed a standard commercial diet.

Under general anesthesia using pentobarbital, a Thomas fistula was constructed in the duodenum of each dog to facilitate the collection of pancreatic juice. At least 10 days elapsed from the time of surgery until testing in order for the dogs to be fully recovered.

Secretin tests were performed in order to determine the pancreatic output in the control period as well as in response to the administration of dDAVP and tGLVP. There was an interval of at least three days between the performance of each secretin test in a given dog.

The secretin tests were performed as follows. Each dog was deprived of food but not water for 16 hours. The main pancreatic duct was cannulated through the Thomas fistula in order to obtain a steady collection of pancreatic exocrine secretion

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TABLE I

MEAN SECRETIN TEST RESPONSES AND STANDARD DEVIATIONS FOR FOUR DOGS IN CONTROL PERIOD AND AFTER TREATMENT WITH dDAVP AND tGLVP

| | Volume cc./kg. | Bicarbonate mEq./kg. | Total protein mg./kg. |
|---|---|---|---|
| Control | 1.92±.37 | .245±.047 | 10.18±3.77 |
| dDAVP 20 ng./kg. | 2.05±.35 | .254±.045 | 14.09±8.35 |
| dDAVP 100 ng./kg. | 2.00±.51 | .260±.062 | 4.22±1.44 |
| tGLVP 100 µg.* | 0.84±.36 | .099±.043 | 10.36±7.33 |
| tGLVP 1 mg. | 0.60±.28 | .027±.061 | 11.71±13.29 |

* Dog #4 received 500 µg. of tGLVP.

uncontaminated by duodenal fluid. Secretin (vitrum) was adminstered at a submaximal dose, 1 U./kg., in an intravenous bolus. The stimulated pancreatic outflow was then collected over a 30-minute period in five-minute specimens.

The volumes of pancreatic juice obtained were measured and the samples analyzed for their bicarbonate and protein contents. Bicarbonate was determined using a Technicon Autoanalyzer II; total protein was measured spectrophotometrically.

For the secretin tests performed in response to dDAVP, the drug was administered intravenously five minutes before the injection of the secretin. The dDAVP was given in two different dosages, 20 ng./kg. and 100 ng./kg., in each dog. In those tests using tGLVP, the drug was given 15 minutes prior to the injection of the secretin, in order for the analog to achieve its peak effect (the inactive hormonogen must be cleaved enzymatically *in vivo* to its active form). Intravenous dosages of 100 µg., 1 mg. and in one dog, 500 µg., were administered.

In a second part of the experiment an attempt was made to ascertain whether the inhibitory effects observed with VP and its analogs were merely a result of a vasoconstriction-induced diminution in the delivery of the intravenously administered secretin to the pancreas. In three dogs, responses to tGLVP were tested as before, but the submaximal dosage of secretin was doubled, using 2 U./kg. In another test, two dogs were given the standard secretin dosage and after five minutes, during the peak of the pancreatic output response when the secretin was presumably already bound to pancreatic receptors, a bolus dosage of LVP (50 µg./kg.) was given intravenously, to determine its effects.*

## RESULTS

The administration of dDAVP in either dosage had no effect on secretin-stimulated pancreatic volume or bicarbonate output as compared with those measured during control periods (Table I and Figs. 1 and 2). On the other hand, tGLVP significantly inhibited both the flow rate (average inhibition 56 and 68% with dosages of 100 µg. and 1 mg., respectively) and bicar-

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*All peptides were supplied by Ferring Pharmaceuticals, Inc., New York.

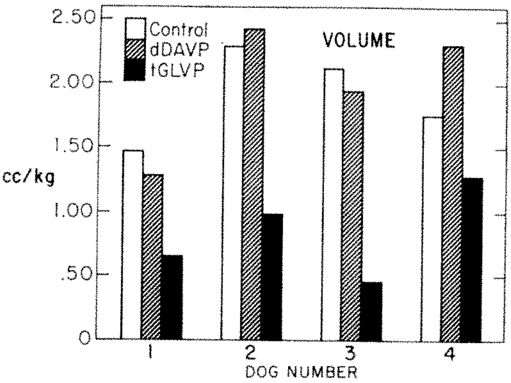

Fig. 1—Volume response of four dogs to intravenous secretin after treatment with dDAVP (100 ng./kg.) and tGLVP (100 $\mu$g.) as compared with the control period.

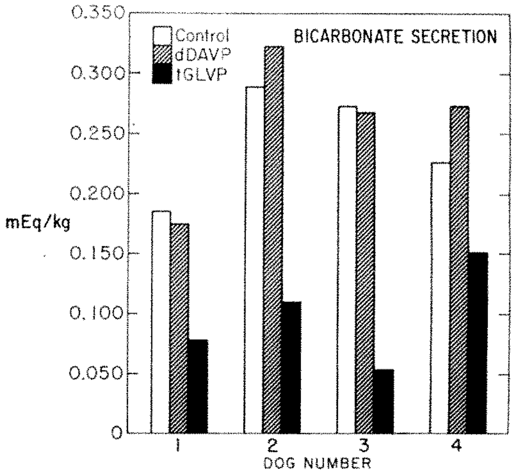

Fig. 2—Bicarbonate secretion in four dogs in response to intravenous secretin after treatment with dDAVP (100 ng./kg.) and tGLVP (100 $\mu$g.) as compared with that of the control period.

bonate output (average inhibition 60 and 89% with dosages of 100 $\mu$g. and 1 mg., respectively). Only dog #4 showed no response to 100 $\mu$g. of tGLVP; she did, however, respond to 500 $\mu$g. (the results of this latter dosage are used in the calculations for this animal).

Protein responses were highly variable. The only apparent trend seemed to be a reduction in protein output following 100 ng./kg. of dDAVP (Table I and Fig. 3).

When the secretin dosage was doubled, pancreatic output, which had been suppressed with tGLVP, recovered almost to control levels (Table II).

In response to the administration of LVP during the peak of the pancreatic response to secretin, there was an abrupt and dramatic diminution in pancreatic output of both volume and bicarbonate (Fig. 4).

## COMMENT

There is general agreement that ADH reduces the exocrine secretion of the pancreas in response to secretin, there being a direct correlation between the amount of VP administered and the degree of pancreatic inhibition.[4, 5] The bicarbonate content of the pancreatic juice is lowered somewhat more than is the volume, while effects on the amylase levels have been variable.[1-3, 6] Despite this unanimity of opinion concerning the effects of VP on the gland, its mode of action is controversial.

VP promotes the retention of water by the kidneys by increasing the permeability of the epithelial membranes in the distal nephron to water, thereby facilitating its reabsorption along an osmotic gradient. VP is also a vasoconstrictor and is known to reduce the blood flow to the viscera.[7] Either of these actions, or a combination of them, might account for the inhibition of pancreatic secretion observed with the drug.

VP has been shown to alter the permeabilities of a variety of epithelial surfaces in addition to that of the kidney tubule, including the toad bladder, frog skin, human sweat glands and salivary glands.[1, 6] It has therefore been surmised that vaso-

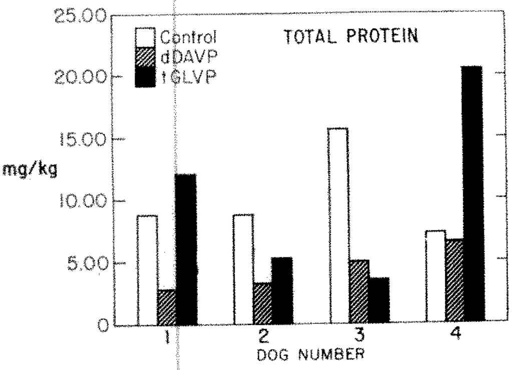

Fig. 3—Total protein output in four dogs in response to intravenous secretin after treatment with dDAVP (100 ng./kg.) and tGLVP (100 μg.) as compared with that of control period.

pressin may influence all organs concerned with the turnover of body fluids, including the pancreas and may act as a general fluid regulating hormone.[6] Although the threshold amount of VP required to affect the pancreas is considerably higher than for the kidney,[4, 6] there is evidence that the endogenous release of VP may be of sufficient magnitude to affect the pancreas, supporting the concept that its effects here are physiological rather than pharmacological.[1, 4]

On the other hand, when Claude Bernard observed that during digestion the pancreas became red and congested, he suggested that the rate of blood flow to the gland might directly influence its rate of secretion.[8] In an extensive review of the subject, however, Tankel and Hollander concluded that there was no evidence to substantiate the belief that inhibition of pancreatic secretion could be caused by a diminution in its blood supply, unless the reduction is so massive that it interferes with cellular metabolism.[9] In fact, several investigators measured the rate of blood flow to the pancreas and failed to note any reduction at all in response to the administration of VP.[4, 10]

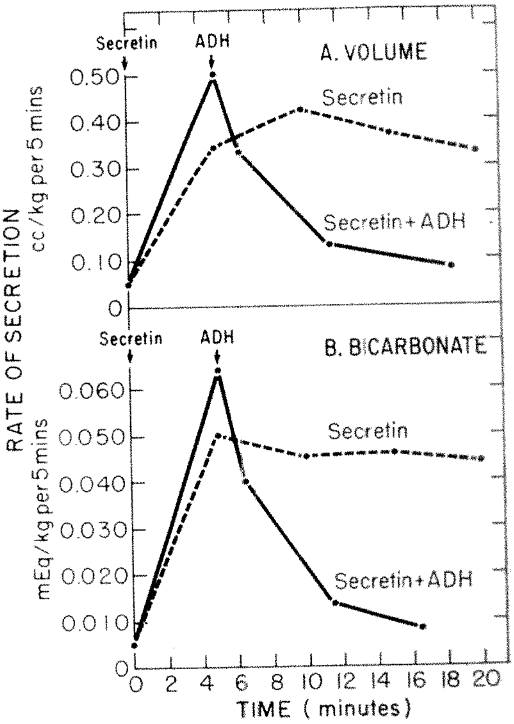

Fig. 4—Postsecretin rates of volume and bicarbonate outputs in response to administration of ADH during peak of response, as compared with control values not receiving ADH.

More recently, with refined isotope clearance technics, other workers have found that pancreatic perfusion is indeed reduced by the administration of VP.[11, 12] In addition, Buranorugna and Moore noted that when pancreatic blood flow is maintained at a constant rate *in vitro*, VP has no effect on its secretion rate, suggesting that it is the lowering of perfusion which accounts for the inhibitory actions of the hormone on the pancreas.[3]

Recently, synthetic analogs of VP have been developed with modified properties of the parent hormone. Two such compounds at opposite ends of the functional spectrum are dDAVP and tGLVP. In dDAVP the hemicysteine at position 1 of VP is replaced by β-mercapto-propionic

TABLE II

MEAN SECRETIN TEST RESPONSES FOLLOWING tGLVP, 100 $\mu$G. I.V. USING STANDARD SECRETIN DOSAGE AND TWICE STANDARD DOSAGE

|  | Volume cc./kg. | Bicarbonate mEq./kg. | Total protein mg./kg. |
|---|---|---|---|
| Secretin 1 U./kg. (standard dosage) | .84±.36 | .099±.043 | 10.36±7.33 |
| Secretin 2 U./kg. | 1.72±.367 | .214±.054 | 10.81±10.03 |

acid and the L-arginine in position 8 is replaced by D-arginine.[13] The result is that dDAVP has a more potent antidiuretic activity, a longer duration of action, and is practically devoid of pressor activity as compared with VP.[14, 15] In the only previous experiment where pancreatic function was examined in response to dDAVP, no change in the volume of secretion was noted following the administration of up to 600 ng./kg. of the drug to anesthetized dogs.[3] The bicarbonate and protein levels of the pancreatic juice were not measured. Our present study confirms that 20 and 100 ng./kg. of dDAVP has little effect on the volume and bicarbonate outputs of the exocrine pancreas in awake dogs. Since this drug has greater antidiuretic properties and was given in dosages of up to 100 times greater than the threshold required for ADH on the pancreas,[5] we surmise that it is not the antidiuretic property of ADH which accounts for its inhibitory actions on this organ. The isolated findings of a lowering of total protein secretion with the higher dosage of dDAVP is not understood and is probably not important, as the protein concentrations measured were in general highly variable.

Triglycylvasopressin is an inactive hormonogen which, when administered intravenously, is gradually converted enzymatically to lysine-vasopressin, the active metabolite.[7, 16] The result is a persistent elevation in mesenteric vascular resistance and therefore a reduction in visceral perfusion,[17] with little antidiuretic effect.[8] When we administered tGLVP to our dogs, we noted a marked suppression in both the volume response and the bicarbonate secretion of the pancreas. This would suggest that it is the lowered perfusion which is responsible for the reduction of pancreatic secretion. This reduction, however, might not be directly related to the diminished blood flow to the parenchymal cells *per se* but could possibly result from a diminution in the rate of delivery of the administered secretin to the gland, secondary to the drug-induced vasoconstriction.

We reasoned that if diminished blood flow delivery of secretin were the cause of the lowered pancreatic response, we should, by doubling the quantity of secretin administered, increase its delivery and thereby the response of the gland. Had there been no augmentation in flow with this additional dosage it would have been clear that delivery was not the critical inhibitory factor. The converse, however, is not necessarily true and although the pancreatic output did rise, it can be argued that increasing the secretin stimulus from its standard submaximal dosage could increase the response even if the inhibitory effect of VP and tGLVP were not one of reduced delivery.

Accordingly, we decided to inject a standard secretin dosage and during the period of maximum pancreatic secretion, at which time the secretin is fixed to its receptors in the gland, we would administer a bolus of LVP. (We could not use the analog here because tGLVP has a gradual onset of action; ADH works immediately.) Pancreatic secretion abruptly and dramatically fell in response to LVP despite the fact that secretin was already delivered, bound and exerting its stimulatory effects. Therefore, we conclude that the inhibitory action of VP as well as of tGLVP on the pancreas is directly attributable to its reduction in the blood flow to the cells of the organ and not merely to a reduction in the delivery of secretin, nor to a direct "antidiuretic" effect on the pancreas.

tGLVP has a prolonged action with few undesired side-effects, and has already been introduced on a trial basis into clinical gastroenterology.[8] The question can be raised whether such a long-acting effect should be tested clinically in such states as pancreatic fistulas, cysts, etc. previous to and during surgical intervention.

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## *Clinical Vignette*

# Scleroderma with Carcinoma of the Esophagus

### CASE REPORT

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Progressive systemic sclerosis (scleroderma) is an uncommon disease with an estimated average annual incidence of 2.7 patients per million and a 3:1 ratio female to male involvement. It occurs with equal frequency in various races.[1] Esophageal involvement with this disease is common and is manifested by reduced peristaltic activity in the body of the esophagus and decreased lower esophageal sphincter pressure. Reflux of gastric contents leads to esophagitis and frequently stricture formation.[2]

Carcinoma of the esophagus occurs with an estimated incidence rate, age standardization to the world population, of below 15.0/100,000 for males and below 5.0/100,000 for females.[3]

This is the fourth report of a patient with both scleroderma and carcinoma of the esophagus.[4-6] It is the first reported occurrence of the two diseases in a male subject with CRST syndrome[7] (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectasia syndrome).

## CASE REPORT

Y. C. was a 48-year old black male who presented initially to the Kansas City Veterans Administration Hospital in 1973 with a five-year history of progressive fatigue,

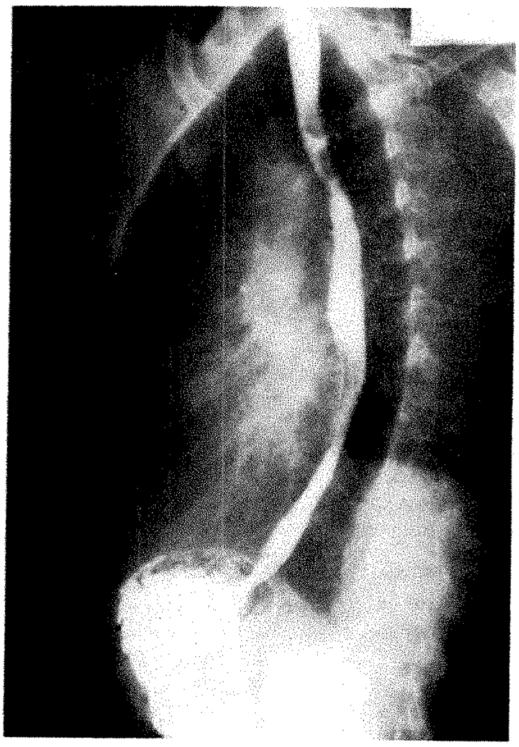

Fig. 1—Dilation of the esophagus with absent peristalsis in the distal two-thirds is characteristic of involvement with scleroderma.

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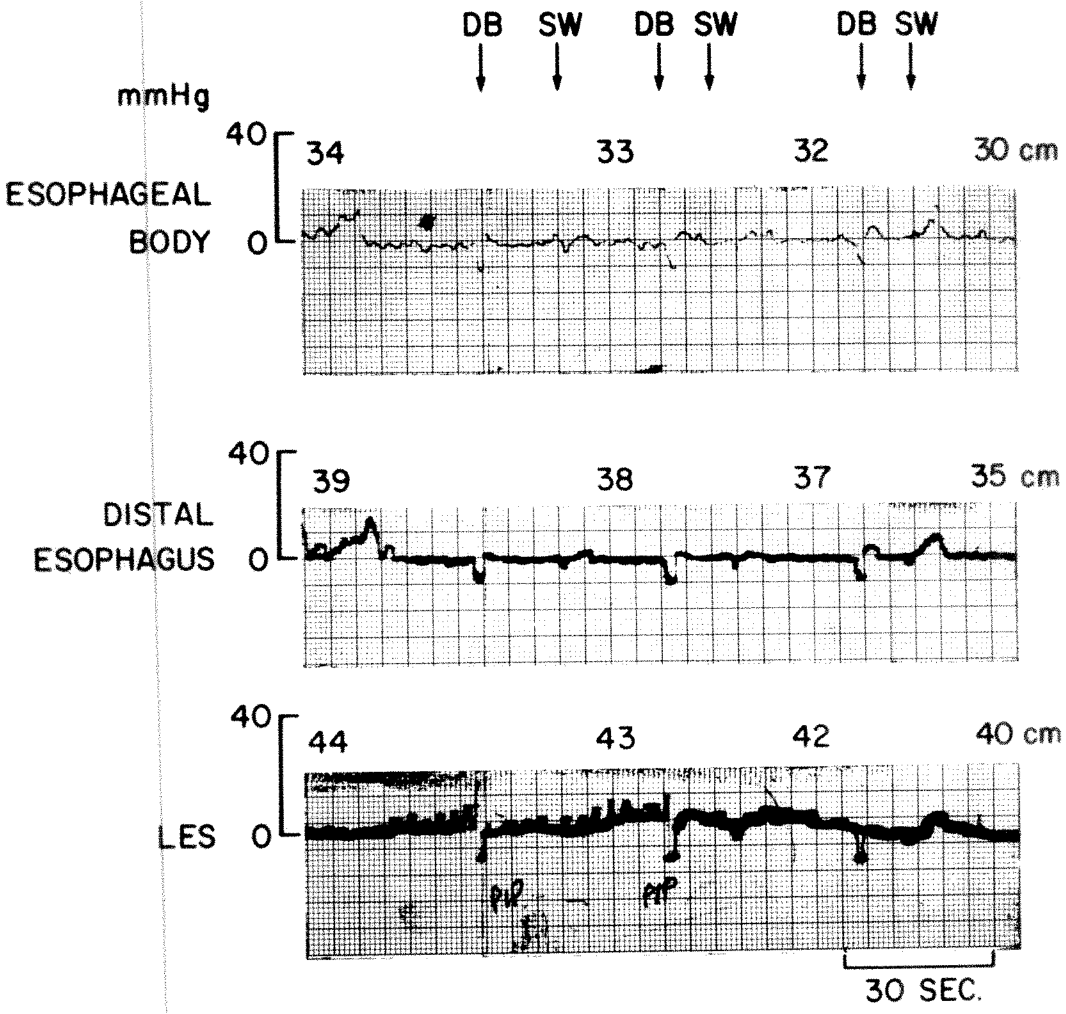

Fig. 2—Esophageal motility tracing confirming absence of peristalsis and diminished lower esophageal pressure.

dyspnea on exertion, pyrosis, Raynaud's phenomenon and contractures of the fingers of both hands. He was found to have thin, atrophic, taut skin over the malar regions and hands, calcinosis cutis and telangiectasis on the tongue. A fixed split $S_2$ with an increase in $P_2$ was heard over the precordium. Laboratory studies included a negative ANA, RA, normal complement levels but an elevated gamma globulin of 3.06 gm.%. Chest x-ray revealed a diffuse finely reticular pattern involving both lung fields. Studies of pulmonary function confirmed a mild restrictive defect with a moderate decrease in diffusing capacity, measuring 9 cc. CO./min.$^{-1}$ mm. Hg.$^{-1}$ A barium swallow disclosed diffusely diminished peristaltic activity of the esophagus which was confirmed by esophageal motility studies (Fig. 1). The LES pressure was 3-5 mm. Hg. (Fig. 2) and the Bernstein test was positive. Mild esophagitis was seen at endoscopy and microscopic examination of a biopsy of the distal esophagus showed focal atypical dyskeratosis. The patient was treated with a vigorous antiesophageal re-

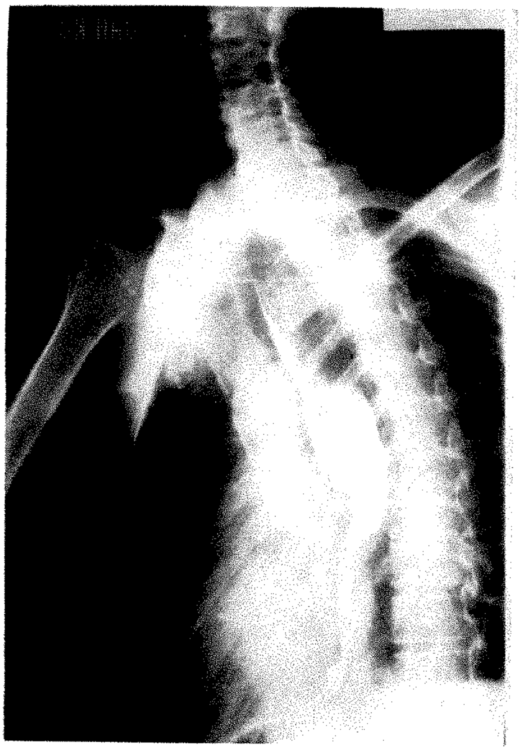

Fig. 3–In 1975 the barium swallow reveals the fungating lesion nearly obstructing the distal esophagus compatible with carcinoma.

flux regimen which included small meals with upright posture for the following two hours, antacids and elevation of the head of the bed.

He was readmitted in 1975, 23 months later complaining of dysphagia. He was able to consume only liquids and had lost 4.5 kg. in the preceding two months. He complained also of nonradiating substernal chest pain relieved by standing and antacids. Physical examination was unchanged. His hematocrit was 37% and guaiac examination of a stool specimen was negative. A repeat barium swallow revealed the mucosal irregularity and stricture depicted in Figure 3. At esophagoscopy, a biopsy of a nodular mass, 30 cm. from the incisors, proved to be a moderately differentiated squamous cell carcinoma (Fig. 4). Due to his relatively poor pulmonary function, he was given 3,240 rads of cobalt irradiation. He did not respond to this therapy and died five months later.

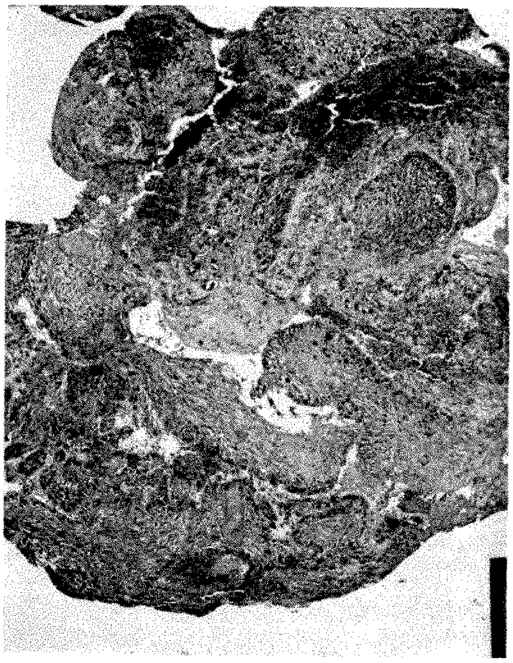

Fig. 4–Esophageal biopsy confirming malignancy (Hematoxylin and eosin, original magnification x60).

## COMMENT

Chronic stasis, irritation and scarring may predispose to esophageal carcinoma. For example, it is known that from 7-29% of patients with achalasia subsequently develop esophageal carcinoma.[8-11] Esophageal lye stricture increases the risk of developing esophageal cancer a thousand-fold.[12, 13] Benign peptic esophageal strictures and surgically induced gastroesophageal reflux with chronic esophagitis have been reported to occur with carcinoma of the esophagus.[14-17] Other recognized associated factors include use of cigarettes and alcohol, Plummer-Vinson syndrome, Barrett's epithelium and tylosis (*hyperkeratosis palmaris et plantaris*). Only three other cases of carcinoma of the esophagus, occurring in patients with scleroderma, have been reported. A comparison of the features of these cases and our own can be seen in Table I.

Statistically the random occurrence of these two diseases in the same host must be exceedingly rare. By chance alone about one in every 7,000 patients with scleroderma might develop carcinoma of the esophagus assuming the same incidence as occurs in the general population. In those cases of progressive systemic sclerosis (PSS) with esophageal involvement reported by Lindsay, no subsequent development of malignancy was noted.[18] Although Tuffanelli reported 19 cases of internal malignancy among his study of 727 cases of systemic scleroderma he did not identify the types of neoplastic lesions which developed.[19] Christianson, Brunsting and Perry found eight cases of malignant neoplasms among 125 patients with systemic scleroderma, seven of whom were female; four had carcinoma of the breast and two had carcinoma of the uterus.[20]

It is accepted that lye and surgically induced gastroesophageal reflux with chronic esophagitis increase the probability of developing cancer of the distal esophagus. One would expect a greater incidence among scleroderma patients with strictures secondary to the chronic reflux. This, however, has not been reported. Possible explanations for the paucity of reported cases are: 1. the relatively short life span following diagnosis of PSS (65% mortality during the first seven years of the disease[21]) precluding development of a carcinoma in the area of chronic stasis and irritation; 2. attributing aspiration (a frequent cause of death in patients with PSS) to esophageal motility abnormalities with decreased LES pressure and possible stricture without closely inspecting the distal esophagus pre- or postmortem, or; 3. lack of thorough

TABLE I

| Case | Date reported | Age | Sex | Race | Duration of dx. PSS | Duration dysphagia when Ca dx. | Esophageal involvement with PSS by | | Survival after dx. eso. Ca. | CRST* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Motility | Ba Swallow | | |
| 1 | Matzner, et al, 1963[6] | 54 | F | Cauc. | 11 yr. | 2.5 mo. | NR | Pos. | 9 mo. | CRS |
| 2 | Kilton, et al, 1971[5] | 44 | F | Black | 1 yr. | 10 mo. | NR | NR | NR | CRS |
| 3 | Johnson, et al, 1973[4] | 60 | F | Cauc. | 11 yr. | 25 yr. | NR | Pos. | 10 mo. | NR |
| 4 | Present case, 1976 | 48 | M | Black | 7 yr. | 2 yr. | Pos. | Pos. | 5 mo. | CRST |

*C = calcinosis; R = Raynaud's phenomenon; S = sclerodactyly; T = telangiectasias; NR = Not reported long-term follow-up in patients with esophageal involvement with PSS.

A relationship between dermatomyositis and malignancy has been well established. Although suggested by some authors, such a relationship has not been established for patients with the connective tissue disease, scleroderma.[22-26] Despite the fact that the esophagus of patients with scleroderma is chronically irritated due to acid reflux (so that stricture is not uncommon), it would appear that the development of carcinoma of the esophagus in these patients probably is a rare event.

## ACKNOWLEDGMENT

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## *Clinical Vignette*

# Unusual Presentation of Pulmonary Inflammatory Pseudotumor (Plasma Cell Granuloma) as Esophageal Obstruction

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A 12-year old boy had a five-year course of dysphagia secondary to lower esophageal obstruction by a posterior mediastinal extension of an inflammatory pseudotumor of the lung. The case illustrates the capacity of pseudotumor to behave in a locally aggressive manner and to present in extrapulmonic sites.

## INTRODUCTION

Inflammatory pseudotumor of the lung is a condition of unknown etiology characterized histologically by large numbers of plasma cells and fibrous tissues. The lesions tend to progress slowly and may lead to embarrassment of pulmonary function in some patients.[1, 2] Uncommon instances of extension of the process beyond the lung[1-4] and similar lesions in extrapulmonary sites[5-8] have been noted. This report describes a 12-year old boy with inflammatory pseudotumor of the lung which also involved the posterior mediastinum and produced esophageal obstruction.

## CASE REPORT

The patient was a 12-year old male who had had the onset of progressive difficulty in swallowing at age seven. There was a vague history of similar difficulty in infancy. At age 10 chest radiograph had shown a mediastinal mass. A gastrostomy was performed and a retrograde esophageal dilatation attempted but without success in relieving the obstruction. Despite feedings through the gastrostomy tube weight loss continued. On hospitalization he was cachectic, anemic and febrile. Chest radiographs showed a mediastinal mass and parenchymal infiltration in the right lower lobe (Fig. 1). Barium swallow demonstrated complete obstruction of the lower esophagus with dilatation of the upper portion. Barium introduced through the gastrostomy showed a normal stomach.

A right exploratory thoracotomy was performed. Bacterial cultures of material from the mediastinal mass were negative. Death occurred on the second postoperative day following an intrathoracic hemorrhage.

Autopsy demonstrated a large mass of dense almost cartilaginous tissue involving in continuity both lower lobes of the lungs and the posterior mediastinum. The mass surrounded and infiltrated the wall of the lower third of the esophagus over about 6 cm. thereby markedly reducing but not

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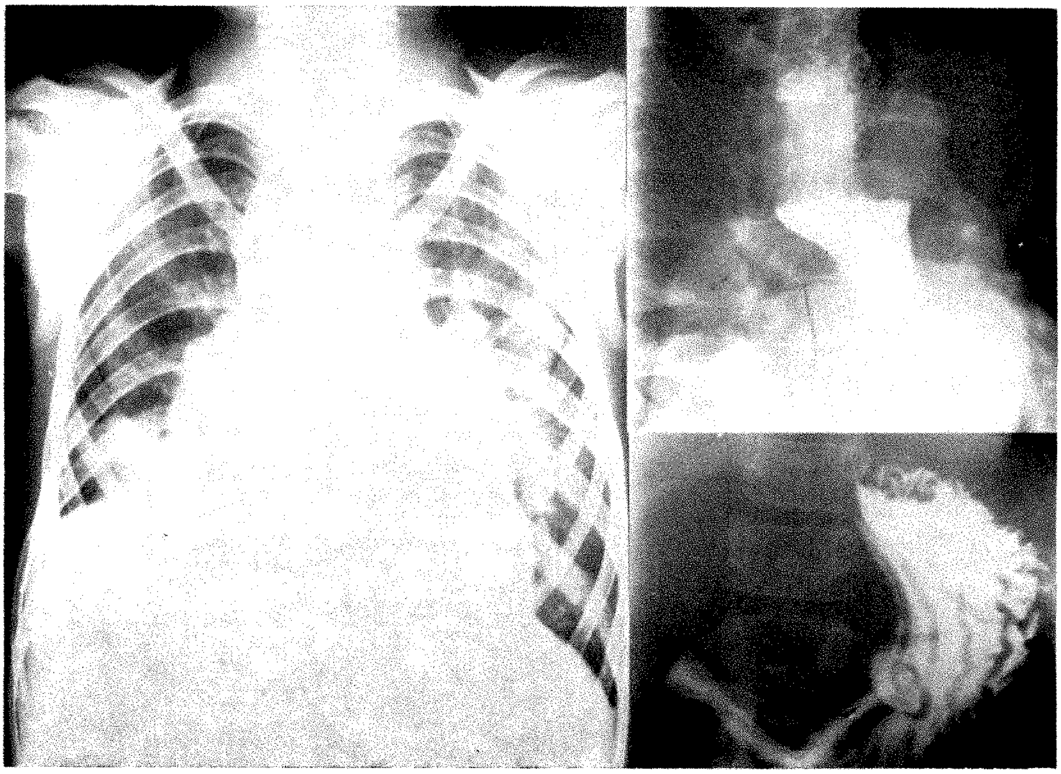

Fig. 1—*Left*: Chest radiograph demonstrating infiltrate in the base of the right lung and widening of the mediastinum. *Upper right*: Barium study of the esophagus showing obstruction at the cardia and marked dilatation of the midesophagus. *Lower right*: Barium introduced into the stomach through the gastrostomy shows no abnormality.

completely obliterating the lumen. The mass of tissue was largest in the right lower lobe extending anteriorly to be adherent to the chest wall and surrounding and obstructing the lobar bronchus. The pericardium was attached to the mass by fibrous adhesions.

Histologically the mass was similar throughout consisting of numerous plasma cells and lymphocytes interspersed in a background of cellular fibrous connective tissue (Fig. 2). Russell bodies were numerous. In some areas the fibrous tissue was predominantly collagen fibers and the cellular elements were scanty. Small bronchi within the lungs had polypoid growths of the tissue within their lumen.

## COMMENT

Inflammatory pseudotumors (plasma cell granulomas) most frequently occur as intrapulmonary lesions confined within the parenchyma of the lung. Although they may occur at any age, they are frequently seen in children and young adults and range in size from lesions measuring only a few centimeters in diameter to large ones occupying one or more lobes of the lung. They are usually asymptomatic and in some instances have been observed to remain stable or increase only slightly in size over long periods of observation.[1] In some patients pulmonary symptoms such as cough, hemoptysis, chest pain or shortness of breath may be present.

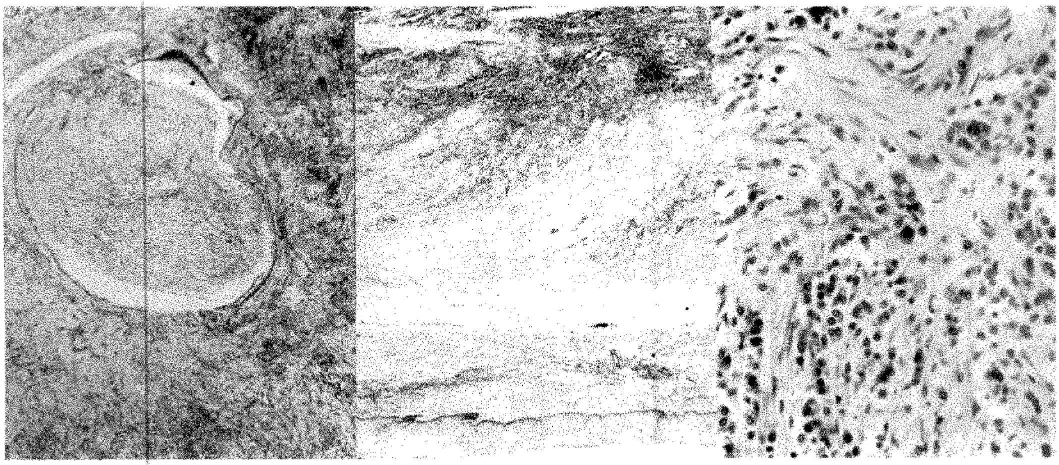

Fig. 2—*Left*: Intrapulmonary inflammatory pseudotumor with infiltration of parenchyma and polypoid extension into a bronchus (Hematoxylin and eosin, original magnification x20). *Middle*: Inflammatory pseudotumor in the lower esophageal wall. The epithelium is intact (Hematoxylin and eosin, original magnification x25). *Right*: Typical appearance of the inflammatory pseudotumor throughout its extent. There are numerous plasma cells in an irregular framework of fibrous tissue (Hematoxylin and eosin, original magnification x400).

Less frequently, the process may extend beyond the confines of the lung to involve adjacent tissue such as the mediastinum[1, 3-4] or the diaphragm.[2] In the case described here the process extensively involved the right lower lobe of the lung but in addition involved the posterior mediastinum and the left lower lobe of the lung. Within the mediastinum the process involved and compressed the esophagus, resulting in dysphagia, while the intrapulmonary component caused no apparent symptoms. As in other cases the process appeared to be an indolent one, in that chest radiographs taken two years before the patient's death demonstrated a mass in the mediastinum and the symptoms of dysphagia, presumably the result of the esophageal involvement, were present for five years prior to death. In many respects this case is similar to Case 17 in the series reported by Bahadori and Liebow[1] in which a lesion in the right lung of an eight-year old boy extended into the mediastinum with involvement of the esophagus and partial obstruction of the superior vena cava resulting in his death.

All attempts to demonstrate the cause of these lesions have proved unsuccessful and the etiology remains unknown. Although the great majority of cases involve the lung, apparently similar lesions have been reported occurring entirely in extrapulmonary sites. Brown and Johnson reported three such cases arising in the pleura[5] and Childress and Adie reported a case confined to the posterior mediastinum[6] which persisted and enlarged following incomplete removal, necessitating a second operation.[7] In addition to these cases occurring in structures adjacent to or near the lung, Soga, et al[8] reported an apparently identical lesion in the gastric cardia of a 33-year old man who experienced difficulty with swallowing for 10 years prior to the successful surgical removal of the mass from his stomach. The etiology of the lesion in these extrapulmonary sites is similarly unknown.

In the case reported here, the inflammatory pseudotumor produced dysphagia due to esophageal involvement and the patient died shortly after attempted surgical correction of this involvement. It is impossible to be certain where the process began in this patient. The large mass of involved tissue in the right lower lobe favors initiation of the process in that site, while the involvement of both lower lobes suggests origin in the mediastinum, a possibility further supported by the long duration of esophageal symptoms. The case thus represents an unusual distribution of this peculiar inflammatory process which proved fatal to this 12-year old boy.

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*Clinical Vignette*

# Fiberendoscopic Removal of Long Foreign Bodies from the Stomach Using a Colon Stiffening Tube as a Protective Sheath

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A colonoscopic stiffening tube was effectively used as a protective sheath in the esophagus during the endoscopic removal of a long ballpoint pen and a writing pencil from the stomach.

The removal of foreign bodies from the stomach by flexible fiberoscopy utilizing biopsy forceps and polypectomy snares has been reported on numerous occasions. We wish to describe the use of a colon stiffening tube in conjunction with a flexible fiberscope to facilitate the removal of two writing instruments approximately 15 cm. in length. This colon stiffening tube allowed us to safely remove these two writing instruments without difficulty or danger of esophageal tear or perforation or provoking operator anxiety.

## Case Report

A TLH 35-88-11, 22-year old, mentally retarded, white woman was referred to our clinic approximately five hours after swallowing a BIC® ballpoint pen. She had swallowed a lead writing pencil, Wallace® No. 4, the previous day. The patient was in no acute distress at the time of examination, which was unremarkable except for her mental deficit and abdominal scars resulting from previous operations for removal of a fork and toothbrush seven months prior and a tongue blade and pencil two months prior to this admission.

After premedication with Cetacaine® spray and 30 mg. of Valium,® endoscopic removal was attempted with an Olympus GIF-D endoscope, biopsy forceps and Cameron-Miller polypectomy snares. The pen and pencil were oriented along the long axis of the stomach with their sharp ends pointed cephalad in the cardia of the stomach. Several attempts to remove the writing instruments, after snaring them by polypectomy snares, were unsuccessful because upon attempting to remove the instruments the points of the instruments would be pulled cephalad and lodge in the esophagogastric junction. Further pressure

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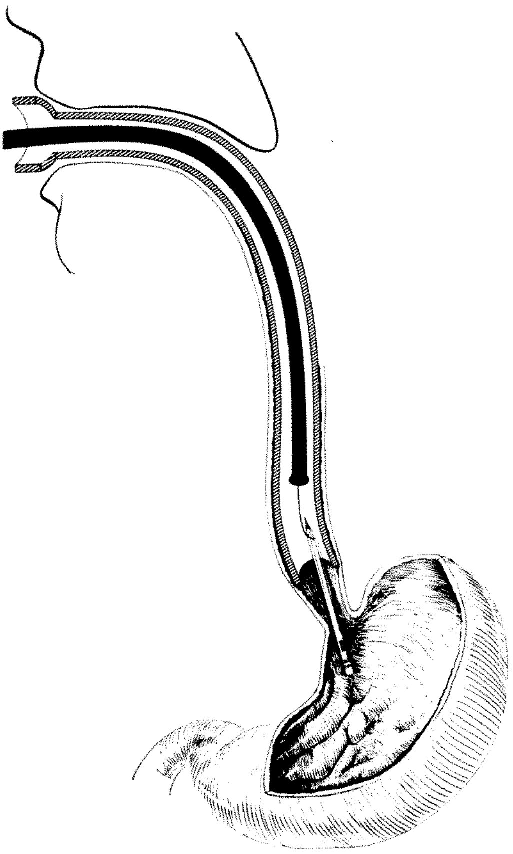

Fig. 1—A pencil is introduced into the colon stiffening tube and the pencil and endoscope are removed simultaneously safely.

would then produce marked distortion of the esophagus with the risk of mucosal tear and hemorrhage. Also, the foreign body forceps could not grasp the sharp end of the pencils tightly for a long time. At this point, the endoscope was removed and an Olympus colonoscopy stiffening device (ST-C1-OD—19 mm. length—40 cm.) was placed over the Olympus GIF-D (14 mm. ext. diameter) upper endoscope. The endoscope was then reintroduced, in the normal manner, with the patient lying on her left side. Upon passage of the endoscope into the proximal esophagus, the patient was then rolled on her back and her neck and head hyperextended and the endoscope then passed further into the esophagus and the colon stiffening tube then passed through the esophagus. The stiffening tube, however, would not pass into the stomach side completely.

The writing instruments were then grasped again with the Cameron-Miller polypectomy snares and maneuvered individually, one at a time, so that the sharp end of the writing instrument was introduced into the distal end of the colon stiffening tube (Fig. 1). The Olympus endoscope and the polypectomy snare holding the foreign bodies were withdrawn and the pen and pencil were removed, one by one, from the stomach without difficulty. Upon termination of the procedure, there was no evidence of mucosal trauma to the esophagus nor was there evidence of further damage to the gastric mucosa. The patient had an uneventful recovery and had no complications from this procedure.

## COMMENT

Fiberoptic endoscopes have been successfully used on many occasions to remove foreign bodies from the esophagus[1, 2] and stomach.[2-7] The utilization of biopsy forceps, grasping forceps, umbilical tape and polypectomy snares to remove objects of varying dimensions have been reported on numerous occasions. The present case is of interest because two linear objects, 15 cm. in length, with their sharp points oriented cephalad in the cardia of the stomach made them difficult, if not impossible, to remove without significant trauma and likely complication.

The use of a colon stiffening tube with its greater external diameter acted both to dilate the esophagus sufficiently to allow the point of the pen to be drawn back into the stiffening tube and as a protective sheath during removal of the foreign body. The use of a colon stiffening tube or a similar sheathing device, utilizing commercially available polyethelene, penrose drain or plastic tubing of appropriate dimensions, is a technic that is readily available and can be utilized to minimize the risk of perforation or laceration when removing sharp or pointed foreign bodies from the stomach or esophagus. Concerning the covering tube for the purpose of foreign body removal, a 3-5 cm. greater length of the tube would permit completely passing the esophagogastric junction.

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***Clinical Vignette***

# Gastroduodenal Fistula or Double Pylorus?

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Acquired anomalies of the pyloroduodenal area are not very common. The congenital anomalies such as pyloric diaphragm, atresia of the duodenum or pylorus and imperforate pyloric web are relatively common.[1] Whether the so-called double pylorus or pyloroduodenal fistula is congenital or acquired is still controversial. We report a case of such a double-barreled pylorus that was proven endoscopically and review some of the recent literature. The purpose of this paper is to familiarize endoscopists with this entity which probably will be encountered more frequently as increasing numbers of endoscopies are being performed for epigastric pain.

## Case Report

D. D. is an 89-year old man first seen in June, 1976 with severe epigastric pain. His gastrointestinal work-up was incomplete at that time because of a complicating subendocardial infarction. One month later he was readmitted to the hospital with increasing abdominal pain and vomiting. He had not been taking any ulcerogenic medication. His past medical history was unremarkable except for chronic alcoholism. A basal cell carcinoma had recently been diagnosed and treated with superficial radiation to the face. The family history was noncontributory, and the review of systems unremarkable.

Physical examination revealed an elderly, poorly nourished, and uncommunicative Italian man. His vital signs were within normal limits and examination revealed bilateral immature cataracts, a hyperpigmented scar on the face, epigastric tenderness, and an organic brain syndrome.

The laboratory data included a normal CBC, SMA/12, urinalysis, protein electrophoresis and coagulation survey. His hemoglobin was 12.2 gm. with normochormic indices. The fasting serum gastrin was 163 pg./ml. (the normal 0-300 pg./ml.).

The chest x-ray was within normal limits and an upper gastrointestinal series showed a 1.5 × 3 mm. ulcer in the gastric

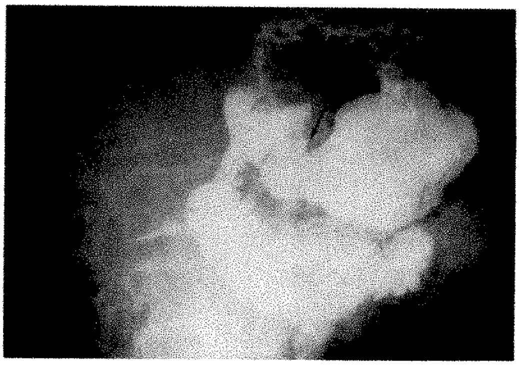

Fig. 1—Upper gastrointestinal series showing the prepyloric ulcer (arrow).

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From the Department of Gastroenterology, Cooper Medical Center.

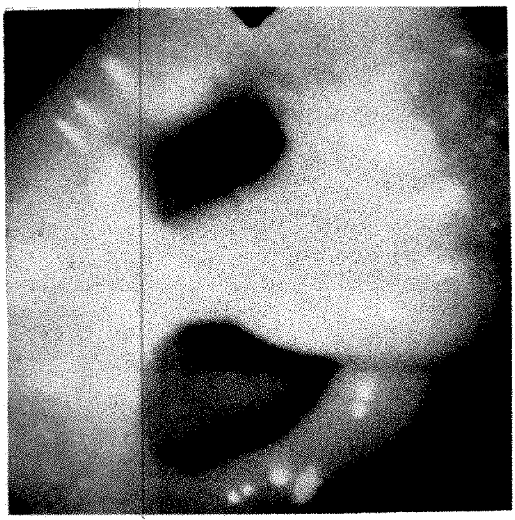

Fig. 2—Endoscopic photograph of the pylorus showing two channels.

antrum with prominent folds radiating from that area (Fig. 1).

The Olympus G. I. F.-K Panendoscope passed easily through the normal esophagus into a small hiatal hernia. At the most distal antrum there was a vertical septum across the pylorus. The appearance was that of a double-barreled pylorus or two pyloruses entering into the duodenal bulb (Fig. 2). A probe could easily be passed through one barrel and seen through the other. An ulcer was noted through the channel closest to the anterior wall of the stomach and duodenum. A biopsy taken from the septum was reported as showing gastric and pyloric mucosa. No tumor could be identified. A repeat endoscopy two weeks later, after he had been on a strict ulcer regimen, showed no changes.

The improvement in his symptoms could not be well assessed because of his mental status. Although surgery was considered, the patient and his family refused, and he was discharged to the care of his family physician. At the time of this writing he is reported by his family to be in good health.

## COMMENT

Two types of gastroduodenal fistulas have been described by Gould[2] in an extensive review of literature. Type I originates from the lesser curvature of the stomach and communicates to the first portion of the duodenum.

Type II begins at the greater curvature of the stomach and communicates to the third or fourth portion of the duodenum. Type III, similar to the one described in this case report, is the so-called pyloroduodenal fistula as suggested by Drapkin, et al.[7] We have found ten well documented cases in the English literature. The summary of their presentations and findings can be seen in Table I.

Rokitansky has been quoted as postulating as early as 1861 that pyloroduodenal fistulas originate from duodenal and gastric ulcers.[3] Ironically enough, he did not report any cases. Among 3,500 consecutive endoscopies Hansen reported four such cases. Kreinsen, et al[1] felt that this is a congenital malformation and that any ulceration seen is more than likely a secondary phenomenon. They support their contention by stating the relative infrequency of pyloroduodenal fistula compared to pyloroduodenal ulcers. Two cases, moreover, were not associated with ulcers.[4] Recently Sufian, et al[10] have reported a case which suggests congenital etiology.

The majority of the patients, on the other hand, were over 60 years of age when they presented with this curious lesion, and the duration of their symptoms was short. Most of the patients did indeed have an active ulcer in close proximity to the fistula. One case was followed endoscopically from the stage of an ulcer to the formation of a septum over a month's period of time.

Whatever the etiology, no specific management has been outlined for patients with

TABLE I

| Author | Patient's age | Symptoms and duration | Endoscopic findings and/or x-ray | Operative and/or pathological findings |
|---|---|---|---|---|
| Smith 1969[6] | 54 | Pain, hematemesis for 3 wk. | 1.5 cm. deep ulcer crater on greater curve and a strip of normal appearing mucosa | Anteroposterior band at surgery.<br>Pathology muscle bundles sandwiched between gastric and duodenal mucosa |
| Hansen 1972[4] | 55 | Epigastric pain for 2 yr. | Prepyloric deformity divided by a mucosal septum; no ulcer | |
| Hansen 1972[4] | 66 | Epigastric pain and vomiting for 3 mo. | Double pylorus and duodenal ulcer on x-ray | Biopsy: pyloric and duodenal mucosa |
| Hansen 1972[4] | 76 | Dyspepsia for 2 mo. | Prepyloric ulcer and pyloric septum | Pyloric mucosa |
| Hansen 1972[4] | 63 | Hematemesis | Prepyloric ulcer and mucosal septum | Pyloric mucosa |
| Drapkin 1974[7] | 64 | Melena | Prepyloric septum and ulceration | Foci of regenerated epithelium with dense cellular infiltration |
| Engle 1975[3] | 76 | Abdominal pain and indigestion | | At surgery, large ulcer with double canal, chronic gastritis, and duodenal ulcer |
| Kreinsen 1975[1] | 69 | Massive hematemesis | | Autopsy: pyloric band; central smooth muscle with gastric and duodenal mucosa; deep ulcer |
| Kreinsen 1975[1] | 61 | Hemorrhage | | Perforated chronic pyloric ulcer communicating with the duodenum; band with central connective tissue and gastric and duodenal mucosa |
| Bender 1975[5] | 57 | Abdominal pain of 20 yr. | Scarred antrum, prepyloric ulcer and septum | |
| Sufian 1977[10] | 30 | Epigastric pain and hematemesis for 7 mo. | Double (pylorus) channel on x-ray | Two channels, no evidence of ulceration; tract lined with gastric mucosa |
| Our case | 89 | Abdominal pain for 2 mo. | Pyloric band and a prepyloric ulcer | Pyloric mucosa on biopsy of band |

pyloroduodenal fistulas. They seem to do well if treated like any pyloric channel ulcer.

It is entirely probable that this lesion is more common than the literature suggests. A double-barreled pylorus will probably be recognized with increasing frequency as direct vision of the pylorus and duodenum is accomplished via endoscopy. As more cases are described, it is very likely that a more complete understanding of the etiology of this curious lesion will be derived.

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***Clinical Vignette***

# Unusual Outcome of Percutaneous Transhepatic Cholangiography*

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In a 72-year old male with fever, mild jaundice and moderate enlargement of both liver and spleen, percutaneous transhepatic cholangiography resulted in direct filling of the portal vein system. Both trunc and left and right hepatic lobe branches showed a typical pattern of incomplete portal vein thrombosis, with mural irregularities and radiolucencies within the lumen. On subsequent operative cholangiography the biliary tract was shown to be normal. At autopsy multiple intrahepatic abscesses of pylephlebitic origin were found. The significance of visualization of the portal vein system during PTC is briefly discussed in comparison with other angiographic technics.

## CASE REPORT

In March, 1973 a 72-year old man was admitted to the hospital with a one-week history of chills, nausea, vomiting and mild jaundice. He also had several months' history of fatigue, anorexia, thirst, sweating and obstipation.

There were no other past or present complaints referred to the abdomen.

On physical examination there was a slight enlargement of both the liver and the spleen. The hepatic area was conspicuously nontender. The abdomen was soft with normal bowel sounds.

Hemoglobin was 8.8 gm./dl. and the white cell count was 8,200/cu. mm. with 86% polymorphonuclears and 12% lymphocytes. Serum bilirubin concentration was 2.4 mg./100 ml. with 1.3 mg./100 ml. conjugated. Serum alkaline phosphatase and transaminase levels were slightly elevated. The urine contained some bilirubin and an excess of urobilinogen.

A chest x-ray examination revealed some elevation of the right diaphragm, with obliteration of the anterior costophrenic angle in lateral view. Plain films of the abdomen only demonstrated an enlarged liver. Excretory urograms and gastrointestinal tract barium studies showed no abnormalities. There was no visualization of the gallbladder or the biliary ducts on I.V. cholangiograms. Multiple filling defects in both lobes of the liver were suspected on the hepatic scintigram. Selective celiac angiography resulted in an unhomogenous opacification of the liver during the capillary phase. In the later venous phase the splenic and portal veins failed to visualize.

At laparoscopy, both lobes of the liver were enlarged; the surface was of a grayish color and showed an irregular relief. The gallbladder seemed quite normal. The

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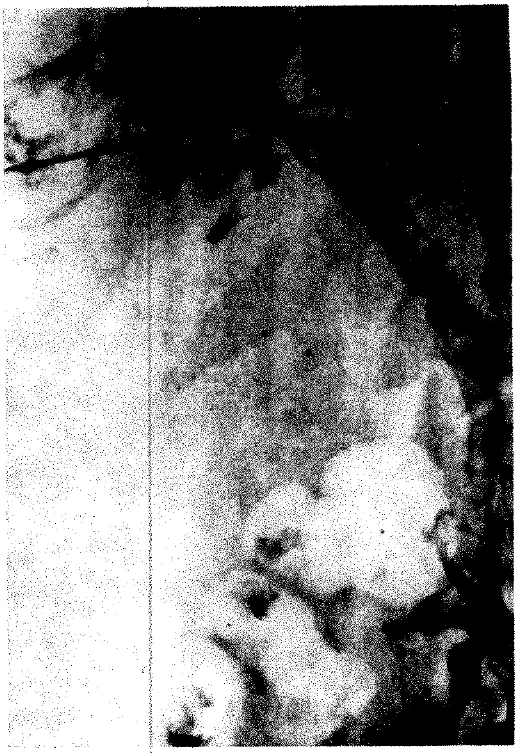

Fig. 1—Structure outlined after injection of contrast medium through PTC needle.

spleen was slightly enlarged, with a few grayish-white spots on the distal margin. Liver biopsy of the left lobe showed a preserved lobular architecture, with enlarged and somewhat irregularly outlined portal tracts, containing an increased amount of connective tissue and a mixed inflammatory cell infiltrate surrounding moderately enlarged bile ducts.

Bile duct proliferation was not conspicuous. Apart from some bile pigment loading in the centrolobular areas, the liver cells appeared normal.

Because of a lack of a definite diagnosis we performed a PTC. On applying gentle suction on the needle, some white viscous substance was aspirated, after which a contrast agent was injected. A rigid Y-shaped structure, lacking the peripheral ramifications and ending distally in some stellate formation, was outlined. (Fig. 1). The irregular deposits and rediolucencies along the wall margins and within the lumen were fairly characteristic for incomplete portal vein thrombosis. We were unable to obtain pictures of the choledochus. At subsequent laparotomy and operative cholangiography the gallbladder and extrahepatic bile ducts were proven to be normal (Fig. 2). Since multiple small abscesses were present in the liver, no attempt at surgical drainage was made. At the time of exploration, no primary suppurative focus was demonstrated. Bacteriological examination of the fluid obtained at PTC showed anaerobic gram-negative organisms.

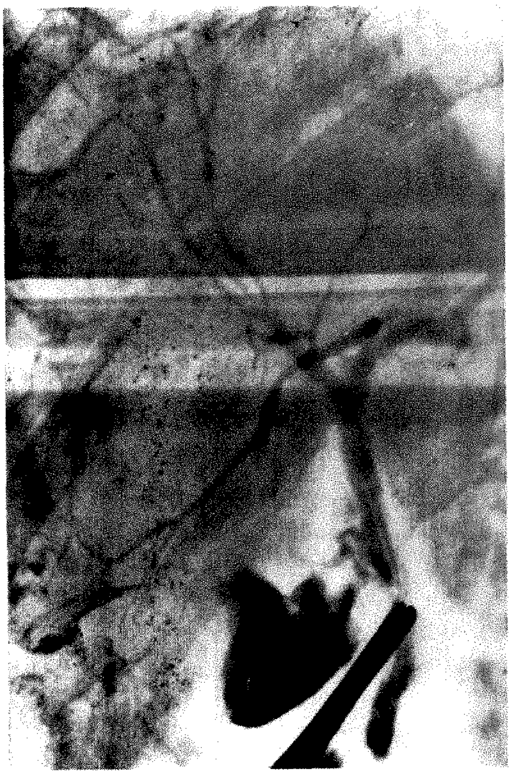

Fig. 2—Operative cholangiogram, showing no gross abnormalities of gallbladder or extrahepatic bile ducts.

Despite intensive antibiotic therapy with ampicillin and gentamicin, the patient deteriorated rapidly and died ten days later.

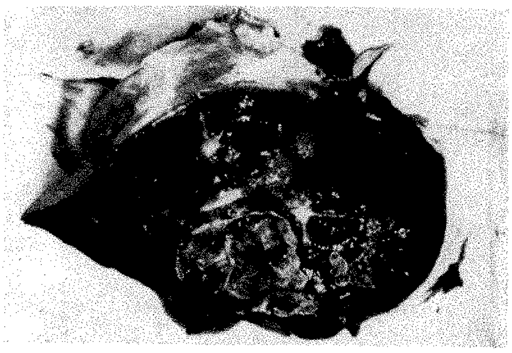

Fig. 3—Cross-section through the right hepatic lobe, showing a large abscess.

At necropsy abscesses of various size were found in the entire liver. On section a large abscess was shown to involve the right lobe (Fig. 3). The portal, splenic and superior mesenteric veins contained pus and thrombi in various stages. The walls were locally weakened and replaced by connective tissue. The spleen was enlarged and on section several zones of necrosis were disclosed. Adhesions were found in the cecal region; the appendix couldn't easily be freed and was grossly replaced by granulomatous and scar tissue, without evidence of abscedation.

## COMMENT

Suppurative pylephlebitis, as a cause of multiple pyogenic abscess of the liver, in this patient was proved to result from appendicitis. The sequence of events was not detected clinically for the patient presented no signs or symptoms of appendicular dissease. At the time of necropsy acute appendicular inflammation had subsided. Pyogenic abscess of the liver of this origin is uncommon now, most cases being a complication of cholangitis.[1]

Hepatic scintiscanning is generally believed to be the procedure of choice when larger liver abscesses are suspected.[2]

Selective arteriography also provides useful diagnostic information.

When portal vein thrombosis is suspected, celiac arterial portography may be performed but sometimes delineation of the portal system is inadequate, so that findings are nonconclusive.[3] Splenoportography or retrograde portography methods can be used supplementarily but are deemed unwise when suppurative pylephlebitis is suspected.

In the present case an incompletely thrombotic portal vein system was unexpectedly outlined at PTC. This method of visualizing the portal vein is principally similar to the technics of retrograde portography by inserting a needle percutaneously through the substance of the liver into an intrahepatic portal vein branch,[4] or by percutaneous intraparenchymal injection of contrast medium.[5]

Both technics require injection of contrast agent under sufficient pressure to produce unphysiologic filling of portal vein radicals and have but few clinical applications.

We certainly do not recommend these methods but simply wish to draw attention to this unusual outcome of PTC.

As far as we know no such result was reported in the literature on PTC and we would like to add "unintended portography" to the pitfalls in diagnosis by this method.

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# State of the Art*

## ENDOSCOPIC ELECTROCOAGULATION OF ACTIVELY BLEEDING ARTERIAL UPPER GASTROINTESTINAL LESIONS

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Emergency endoscopy to find the site of upper gastrointestinal bleeding is now accepted as the diagnostic method of choice. Endoscopic electrocoagulation in uncontrolled series has been successful in 98% of patients so treated (142 of 147). If a vessel is seen in an ulcer bed, some preliminary data would support surgical treatment. In my opinion, electrocoagulation is favored to prevent further bleeding. While some physicians have found electrocoagulation safe and effective, there are some who remain guardedly cautious. In the near future, a multicenter randomized study will begin to further assess the usefulness, effectiveness and safety of endoscopic electrocoagulation. Endoscopic electrocoagulation has opened a Pandora's box to exciting research in finding ways of treating acute upper gastrointestinal hemorrhage. Currently, electrocoagulation is the front runner.

It is exciting to be part of an era which has attacked the problem of endoscopic control of upper gastrointestinal bleeding with such great enthusiasm. Without the development of the end-on viewing panendoscope in the late 1960's and the manufacture of electrocoagulation monopolar probes, the era of electrocoagulation would not have come about as rapidly as it has.

Youmans, et al[1] used a cystoscope through a gastrostomy to cauterize a bleeding vessel in a malignant ulcer in one patient and multiple "stress ulcerations" in another. Shortly afterwards, Blackwood and Silvis[2] voiced concern that cauterization with the Bovie electrosurgical generator may actually cause an increase in bleeding. They proceeded to pursue electrosurgery in the laboratory.[3, 4] I had the experience of using the Cameron-Miller monopolar electrocoagulation probe to successfully coagulate an actively bleeding vessel in a desperately ill patient.[5] The effect was so dramatic that I also began to study electrocoagulation in the laboratory.[6, 7] Sugawa, et al[8] also began electrocoagulation studies about this time. Intensive in-depth work on electrocoagulation and other modalities has been pursued in Dr. Cyrus Rubin's laboratory aimed at defining the safest mode of therapy in upper gastrointestinal bleeding.[9-12] Although numerous other modalities are being studied[10, 13-25] electrocoagulation in the United States has had the widest clinical use with remarkable success.[5, 8, 26-29]

Gaisford[27] initially reported 20 patients successfully treated via electrocoagulation. He now has treated 71 patients with active bleeding by endoscopic electrocoagulation with 92% permanent hemostasis after one treatment. No complications occurred as a result of electrocoagulation. Six patients rebled. Four had repeated successful electrocoagulation for bleeding benign gastric ulcers. One patient with a Mallory-Weiss tear and one with a gastric leiomyosarcoma went to surgery because of persistent bleeding. The lesions electrocoagulated by Gaisford[28] are as follows: esophageal ulcers, 4; Mallory-Weiss tears, 6; gastric varices, 2; gastric ulcers, 29; erosive gastritis, 8; gastric polyps, 2; gastric leiomyomas, 2; pyloric channel ulcers, 3; duodenal ulcers, 13 and jejunal ulcers, 8.

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Sugawa[8] has treated six patients with electrocoagulation with initial success in all. The lesions were as follows: Mallory-Weiss tear, 1; gastric ulcer, 1; gastric erosions, 3; gastric polyp, 1. One patient with gastric erosions and one with a gastric ulcer rebled and required surgical treatment.

Volpicelli[26] has had success in stopping active bleeding in 12 patients initially (duodenal, 6; gastric, 5 and esophageal ulcer, 1). One patient rebled from a gastric ulcer and was successfully re-electrocoagulated. Elective surgery was performed without difficulty one day later.

I have had the opportunity to electrocoagulate 58 patients with actively bleeding lesions on 60 occasions (gastric ulcers, 24; duodenal ulcers, 20; Mallory-Weiss tears, 11; miscellaneous, 3). Three patients were unsuccessfuly electrocoagulated (Mallory-Weiss tears, 2 and duodenal ulcers, 1). The average age of the patients with gastric ulcers was 64 with 15 of 20 patients older than 60 years. The average age in the duodenal ulcer group was 70 with 15 of 20 patients older than 60 years. In the Mallory-Weiss group of patients, the average age was 56 years. Many of the patients in this study had multiple medical problems and were hospitalized in the intensive care units. Nine of 58 patients in this study died. None died from the lesion causing the initial gastrointestinal hemorrhage. No morbidity or death was ascribed to electrocoagulation. Three of the nine died several weeks later on other hospital admissions. Two died from carcinomatosis and one from a gastrosplenic fistula.[29] Therefore, a mortality of 10.3% occurred in this study group (six of 58 patients). This figure compares quite favorably to the figures in other studies which show an increased mortality with increasing age,[30] for emergency operations in patients greater than 70 of 50%,[31] 20-50% in the report of Himal, et al,[32] and 20-60% in other series.[33] In fact, only three patients had to have emergency surgery and they all survived.

It is the intent of electrocoagulation to stop active bleeding so that an emergency can be handled in a nonemergency manner allowing us to stabilize the patient. It is not the intent of electrocoagulation to heal or cure the cause of bleeding. Appropriate management should be decided on an individual basis for a particular patient. Ten of the 58 patients in this series (17%) had surgery.[29] Three of the ten went to surgery as an emergency and seven electively. One of the seven died postoperatively continuing to bleed from a duodenal ulcer. It should be emphasized that all of the 58 patients would have had surgery had not electrocoagulation been used first. Thus, 48 patients avoided surgery and 52 left the hospital alive. It is quite clear that a significant decrease in surgical mortality occurs when a patient with upper gastrointestinal bleeding is operated upon electively rather than as an emergency.[34-37]

It is not surprising that six patients rebled (within 48 hours) on seven occasions. Four had surgery with one postoperative death. Two patients were successfully re-electrocoagulated and one patient had a cardiac arrest before surgery 12 days after her first bleed. Rebleeding in nonsurgically treated patients ranges from over 25-77%.[38, 39] Why do patients rebleed? I have asked myself this question many times. Several years ago I became interested in

TABLE I

RETROSPECTIVE COST ANALYSIS BETWEEN HOSPITALIZATION FOR TREATMENT BY ELECTROCOAGULATION AND MEDICAL AND SURGICAL TREATMENT

| | Hosp. days | Electrocoagulated | Hosp. days | Surgical medical |
|---|---|---|---|---|
| Mallory-Weiss tear | 11 | | | |
| Total | | $1,400 | 29 | S. $5,311 |
| Laboratory | | | | 1,175 |
| Gastric ulcer | 11 | | | |
| Total | | $1,202 | 16 | S. $1,778 |
| Laboratory | | 214 | | 306 |
| | | | 18 | M. $1,956 |
| | | | | 493 |
| Marginal ulcer | 5 | | | |
| Total | | $ 641 | 15 | M. $2,394 |
| Laboratory | | 221 | | 673 |
| | | | 16 | S. $3,662 |
| | | | | 665 |
| Duodenal ulcer | 11 | | | |
| Total | | $1,463 | 9.5 | S. $2,188 |
| Laboratory | | 532 | | 869 |
| | | | 16 | M. $1,710 |
| | | | | 409 |

what happens to vessels seen protruding in a gastric or duodenal ulcer bed. They all seemed to rebleed. Therefore, I followed seven consecutive patients with vessels in their ulcers and found that five rebled and two did not.[40] Subsequently, eight similar patients were randomized to medical treatment (4) and electrocoagulation (4). The four electrocoagulated did not rebleed and progressed to complete healing but the four treated medically rebled, three went to surgery and one was electrocoagulated with cessation of bleeding. The cost of hospitalization and days in the hospital was less in the electrocoagulated group. Griffiths, et al[41] also recognized that visible vessels in ulcers required more transfusions and had an increased mortality. They suggested early surgical treatment. I would agree that the visible vessel patient is one that will rebleed but I would disagree with referral to surgery. Electrocoagulation should be used first. It seems that vessels greater than 2 mm. will not be suitable for electrocoagulation and will require surgical ligation. It is too much to expect that all actively bleeding arterial lesions will stop with electrocoagulation. It is hoped, however, that the majority will. Based on my experience,[5, 29, 40] and that of Gaisford,[27, 28] Sugawa[8] and Volpicelli,[26] I would disagree with Logan and Finlayson[42] that endoscopy doesn't reduce mortality from upper gastrointestinal bleeding. If they had had a mode of therapy as endoscopic electrocoagulation, they might not have lost nine of 64 patients in their series from exsanguination.

In an attempt to determine if total cost and length of hospitalization was altered by electrocoagulation treatment, a retrospective analysis was done as is shown in Table I. The patients with Mallory-Weiss tears treated with electrocoagulation were hospitalized 11 days at a cost of $1,400, one-third the length and cost of the surgically treated patients. Both the gastric and marginal ulcer group of patients treated by electrocoagulation showed a substantial reduction in hospital days and total cost. Surgically treated duodenal ulcer patients were hospitalized on an average of 9.5 days compared to the electrocoagulation group of 11 days but total cost was less when treated with electrocoagulation.

My technic of electrocoagulation of actively bleeding vessels has been previously described.[29] In my opinion it is important not to directly coagulate the vessel but to place the coagulation electrode as near to its base as possible. Gaisford's technic[28] and mine differ in this respect. I feel it is important to coagulate the vessel in the submucosa. One must be careful not to coagulate for too long a duration. Some guidelines from dog work have established safe durations of time and settings for electrocoagulation.[6, 7] Excess pressure should be avoided but firm contact with mucosa is important. Perhaps information acquired from an analog computer recently received from Drs. Cyrus Rubin and David Auth will supply data as to joules of energy actually used over a period of time to stop bleeding with electrocoagulation. A site of coagulation is never coagulated more than once.

Numerous articles have been written regarding the use of a bipolar electrocoagulation vs. monopolar.[43-44] Monopolar electrocoagulation is favored because it is the intent of this technic to coagulate a vessel deep in the submucosa or in the muscular area as it branches upward toward the ulcer base.

There is absolutely no question that endoscopy in the patient with acute upper gastrointestinal bleeding is the diagnostic method of choice. Endoscopy has clearly been shown to be superior to x-ray in identifying the actual site of bleeding in several studies.[45-48] In my series of 58 patients actively bleeding, all the sites of bleeding were identified. There is no substitute for seeing the site of bleeding.

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# The Pediatric Corner

## RECURRENT ABDOMINAL PAIN: APPARENT ASSOCIATION WITH ANNULAR PANCREAS

WILLIAM M. LIEBMAN, M.D.
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Annular pancreas is an uncommon condition in children. A case of annular pancreas, apparently presenting as recurrent abdominal pain only, in a 13-year old girl is discussed.

Annular pancreas has been an uncommon condition in children, presenting as partial or complete duodenal obstruction.[1-5] This report is a case of annular pancreas, apparently presenting as recurrent abdominal pain (RAP) only without obvious obstruction.

### CASE REPORT

A 13-year old girl developed recurrent mid abdominal pain of one and a half years' duration prior to evaluation. The pain was intermittent, lasting minutes to one and a half hours. The pain was not related to meals, food types, position, time of day, or bowel movements. Sleep was not initially disturbed. Nausea, vomiting, bowel habit alteration, fever, anorexia, or weight loss were not present. On admission, she was alert and in no distress, with normal vital signs. Physical examination, including the abdomen, was unremarkable.

Laboratory studies, including serum and urine amylase, serum lipase, serum calcium and phosphorus, SGOT and SGPT, were normal. Upper gastrointestinal series on two occasions revealed a minimal extrinsic defect on the lateral aspect of the second portion of the duodenum with intact mucosa (Fig. 1, arrow). Her subsequent clinical course was characterized by continued, disabling pain, resulting in anorexia, decreased activity, sleep loss and absence from school. Fiberoptic upper endoscopy to the proximal aspect of the second portion of the duodenum was unremarkable. Subsequently, an exploratory laparotomy was performed, revealing an annular pancreas. A duodenoduodenostomy was performed. Postoperatively, she has been free of abdominal pain during follow-up of 19 months.

### COMMENT

Recurrent abdominal pain (RAP) is a common, troublesome problem in chil-

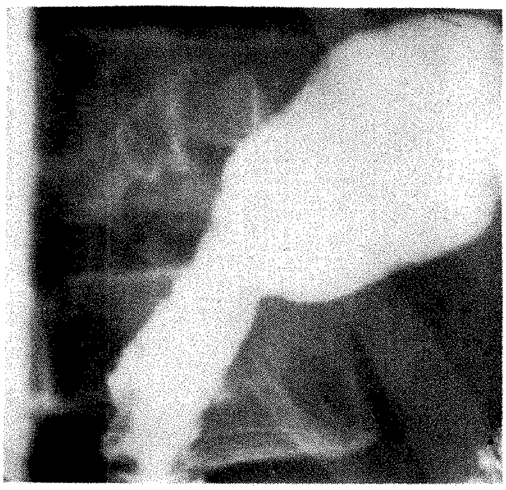

Fig. 1—Upper gastrointestinal series. Minimal extrinsic defect (arrow) is shown on lateral aspects of the second part of the duodenum.

dren. The RAP syndrome consists of at least three attacks of pain, affecting activity, and occurring during a period of time longer than three months.[6] The incidence of RAP in children is 9-15% with girls slightly outnumbering boys.[6] Organic causes have been estimated to be only 6-20%.[6] Although uncommon in children, annular pancreas is not an infrequent cause of upper intestinal obstruction in neonates.[1-4] Regurgitation or vomiting occur or, initially, meconium stools, are usually passed through. A similar obstructive pattern of variable intensity may be evident in older children. Some patients, however, may not have significant difficulty during childhood at all.[1, 2] Particularly, RAP, without apparent obstruction clinically, has rarely been appreciated.[7] Treatment of this condition is surgical, either a duodenoduodenostomy or duodenojejunostomy.[2, 5]

The present case represents an uncommon condition in children, annular pancreas, apparently presenting in a unique manner, recurrent abdominal pain only, and relieved by subsequent surgical treatment.

## ACKNOWLEDGMENTS

Dr. A. Smith provided technical assistance and Mauri Marcy gave secretarial assistance.

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# The Radiology Corner*

## CECAL VOLVULUS

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Cecal volvulus is not a common cause for large bowel obstruction in the United States. Yet when it occurs, prompt surgical treatment is essential and delay for even hours in arriving at the diagnosis will decrease a patient's chance for survival.[1] Roentgenograms of the abdomen and colon are essential for arriving at the diagnosis. It is the purpose of this report to review the roentgen signs of cecal volvulus and also to discuss how they can be used to predict the anatomy of the volvulus.

### ANATOMY OF VOLVULUS

The term "cecal volvulus" is actually a misnomer as much more than the cecum is

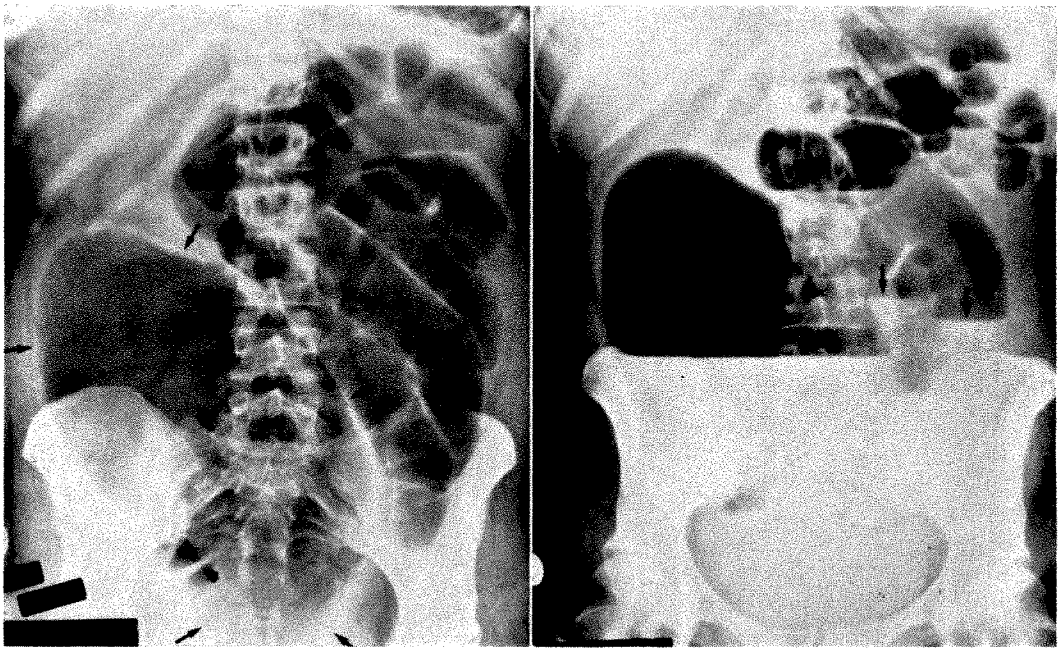

Fig. 1—Axial type of volvulus with 180° (probable) rotation. *Left:* supine film of the abdomen. *Right:* upright film of the abdomen.

The dilated cecum is visualized as a gas-filled structure which is smooth in outline (long arrows). Note only one long air-fluid level on the upright study in the obstructed cecum. The small bowel is distended with differential air-fluid levels (long arrows). The ileocecal valve is positioned laterally (short arrows).

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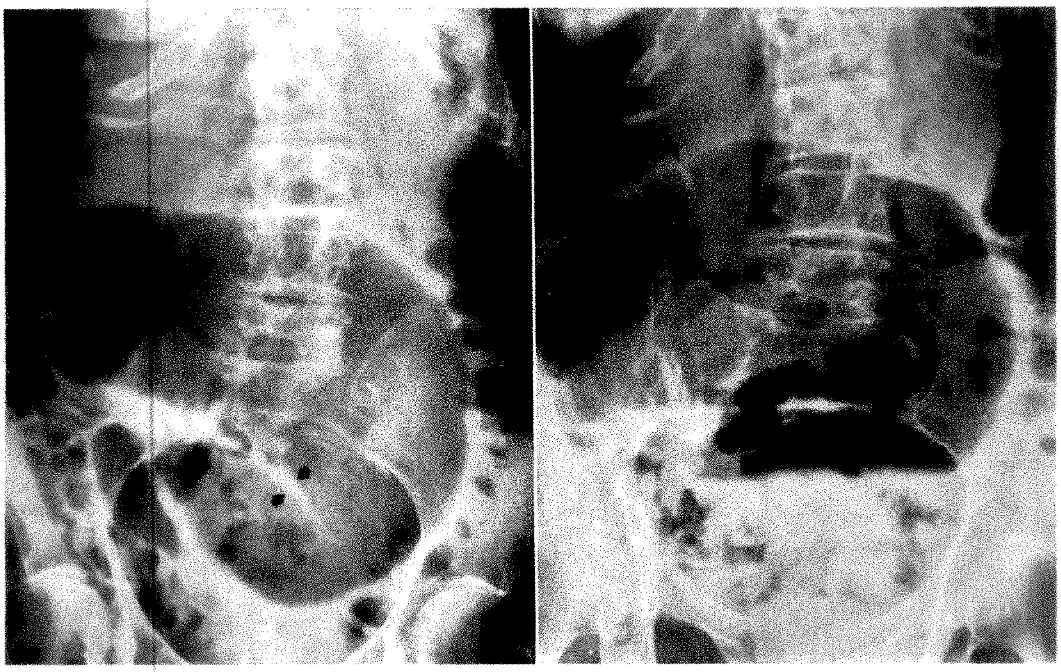

Fig. 2—Loop type of volvulus with 360° or 720° rotation. *Left*: supine film of the abdomen. *Right*: upright film of the abdomen.

The cecum and ascending colon are distended with gas. The maximum diameter is 12.5 cm. On the upright film, two long air-fluid levels are demonstrated. The inferior one is in the cecum while the superior is in the ascending colon. Also visible on the upright film are haustra in the ascending colon (long arrows). Gas-filled small bowel is situated laterally to the twisted loop. The ileocecal valve is positioned medially (short arrows) indicating the twist either 360° or 200°.

involved in the twist. In fact, the entire colon from the cecum to the splenic flexure may be involved in the torsion. Also included in the twist may be the terminal ileum. Thus, the term, "volvulus of the right colon" would be much more appropriate,[2] yet the other name has persisted.

The basic abnormality in cecal volvulus is a rotation of the bowel which results in a partial or complete luminal obstruction. The rotation may occur in a transverse, oblique or parallel plane to the longitudinal axis of the bowel.[2] Rotation is usually in a clockwise direction.[1, 2] Colonic rotation will usually occur close to a point of fixation. In fact, such a fixation point generally serves as a fulcrum for the torsion.[3] Torsion usually occurs at a single point, but a second point of torsion may coexist.[3]

At least 180° of torsion is necessary to produce a luminal obstruction. Most patients with obstructive cecal volvulus, however will have higher degrees of torsion. It is probably also correct to assume that how obstructing a volvulus is depends also upon the tightness of the twist, not merely on the number of turns.[4]

In addition to torsion, displacement of the cecum will occur in most patients with cecal volvlus. Yet, when the cecum is less mobile, rotation parallel to the longitudinal axis alone may occur. Such axial rotation without cecal displacement has been the "sac-type" volvulus.[3, 5] Most cecal volvuli

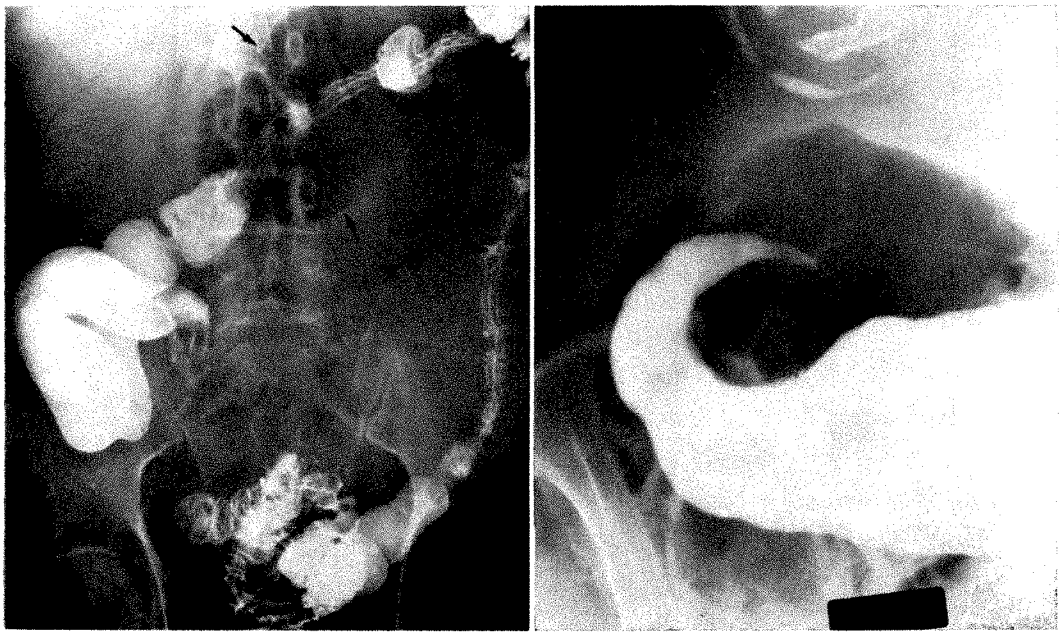

Fig. 3—Loop type of volvulus with displacement of the cecum into the left upper quadrant. *Left*: evacuation film from a barium enema. *Right*: detailed view of the obstruction point demonstrated on the barium enema.

Complete obstruction to retrograde flow is demonstrated in the mid ascending colon. The obstruction point has a tapered or "beaked" appearance and the dilated colonic loop is demonstrated in close proximity. Although some mobility of the distended cecum was demonstrated on sequential films, it was primarily found in the left upper quadrant (long arrows). The ileocecal valve is situated on the superior surface (short arrow) indicating a twist of 540° which was confirmed at surgery. This patient, a physician, presented only a few hours after developing symptoms and thus the diagnosis was made early. This explains why the small bowel is not distended.

are, however, of the "loop type". In these patients, the cecum is much more mobile, the fixation point is more proximal, usually at the hepatic flexure, so that when rotation occurs there is concomitant displacement of the cecum out of the right lower quadrant.[3, 5]

## ROENTGEN FEATURES

The dilated cecum is visible on plain abdominal films, usually as an air-filled loop which is smooth in outline (Fig. 1). Its diameter can be several times that of normal. If the torsion is axial in type, then the distended cecum will remain in its normal position. If it is of the "loop type", the cecum will be displaced out of the right lower quadrant. It may be found in any area of the abdomen but it is most frequently in the left upper quadrant.[3, 5] Haustra may be recognized in the distended loop when colon, proximal to the ileocecal valve, is involved in the twist.[3]

The ileocecal valve can be identified as a "V-shaped" structure on plain films. Its position can be used to predict the degree of torsion. Thus, if it is located medially in an axial type volvulus, the torsion of the cecum is 360° or 720°. In a loop type of volvulus, when the ileocecal valve is on the inferior margin of the displaced cecum, the twist is 180°. If it is on the superior margin, the twist is 360°.[3]

Only one long air-fluid level will be visualized in the distended cecum on the upright study in an axial type of volvulus. On the other hand, if more proximal torsions of bowel are involved in the twist, two long fluid levels will be visualized.[3] (Fig. 2).

The small bowel will be distended unless the obstruction is detected early or it is incomplete. The distended small bowel is frequently located to the right of the obstructed loop. The colon distal to the twist will be empty unless the torsion obstructs the lumen only partially.[3, 5]

Serial films will show increasing dilatation of the twisted loop over hours and days. Its position may vary from film to film.[3]

A contrast enema will be definitive for arriving at the diagnosis. An obstruction will be demonstrated immediately adjacent to the dilated, twisted loop. Sometimes the torsion will be demonstrated by twisted mucosa folds at the obstruction point.[5] (Fig. 3).

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# The Last Page

## QUESTIONS IN GASTROENTEROLOGY

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*The Last Page* appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the article can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. BACTEREMIA FOLLOWING ENDOSCOPY:

   A. Has been described following esophageal dilatation, upper endoscopy, sigmoidoscopy, colonoscopy and barium enema.

   B. Trauma to the bacteria-rich oropharynx may be an important source.

   C. The incidence of bacteremia after ERCP is higher than with other procedures.

   D. Prophylactic antibiotics should be given to patients with valvular heart disease, or to those with pancreatic or bile duct obstruction undergoing ERCP.

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2. NEEDLE ASPIRATION BIOPSY OF THE PANCREAS:

   A. Is used for patients with a pancreatic mass demonstrated by echography.

   B. Is best performed with a fine needle guided by a special ultrasound pilot transducer.

   C. Ensures that the needle does not pass through the gastrointestinal tract or the liver.

   D. Has the same complication rate and mortality as surgical wedge biopsy.

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3. CARCINOMA OF THE PANCREAS:

   A. Its incidence has not increased over the past decade.

   B. Despite lowered mortality of surgical resection, long-term survival has not improved.

   C. Risk factors include race, diabetes, smoking and gallstones.

   D. Earlier diagnosis using sonography, CAT, radionuclide scanning, cytology and needle biopsy, will not necessarily increase survival.

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4. RETROGRADE PROLAPSE OF THE STOMACH:

   A. Is a common occurrence when the lower esophageal sphincter is lax.

   B. May result in acute hemorrhage if it occurs repeatedly during severe retching.

   C. Results in a Mallory-Weiss type of mucosal tear, which is the cause of the bleeding.

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D. May involve all layers of the stomach if the gastrohepatic ligament is redundant.

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5. BRUCELLA CHOLECYSTITIS:

A. Acalculous cholecystitis due to systemic infection is more common in adults than in children.

B. It is more commonly due to Salmonella than to brucellosis.

C. Granulomas are found in the gallbladder in half the cases of brucella cholecystitis and may also be found in the liver.

D. A positive blood culture for *Brucella* is a quicker method of diagnosis than the agglutination test.

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6. INTRINSIC DUODENAL OBSTRUCTION OF THE NEWBORN:

A. May be due to atresia, septum or stenosis.

B. The presenting symptom, vomiting, appears in the second week of life in three-quarters of the cases.

C. Associated congenital anomalies occur in 70% of cases.

D. Mongolism was associated with a higher surgical mortality after duodenoduodenostomy than after other congenital anomalies.

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7. VASOPRESSIN INHIBITION OF PANCREATIC SECRETION:

A. Vasopressin diminishes the volume and biocarbonate secretory responses of the pancreas to secretin.

B. Synthetic analogues of vasopressin are available with predominantly antidiuretic or predominantly vasoconstrictor effects.

C. The antidiuretic analogue reduces secretin by acting on pancreatic ductal epithelium.

D. The vasoconstrictor effect of vasopressin reduces pancreatic secretion by reducing blood flow to the organ.

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8. SCLERODERMA AND CARCINOMA OF THE ESOPHAGUS:

A. Esophageal involvement in the CRST syndrome includes reduced peristalsis, decreased LES pressure, reflux esophagitis and stricture.

B. Achalasia, lye and peptic strictures increase the risk of cancer as much as does scleroderma.

C. Nonesophageal cancer in systemic sclerosis (PSS) is less common than esophageal cancer.

D. Aspiration due to esophageal involvement is a frequent cause of death in PSS.

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9. INFLAMMATORY PSEUDOTUMOR OF THE LUNG:

A. Has no known etiology and is composed of plasma cells and fibrous tissue.

B. Is usually asymptomatic even when very extensive.

C. May invade the mediastinum and obstruct the esophagus.

D. Similar lesions do not originate in extrapulmonary sites.

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10. FIBEROPTIC REMOVAL OF FOREIGN BODIES FROM THE STOMACH:

A. Instruments used have been biopsy forceps, grasping forceps, polypectomy snares and umbilical tape.

B. Long sharp objects may be caught at the esophagogastric junction during attempted extraction.

C. A colonoscopy stiffening tube passed over the endoscope may dilate the esophagus sufficiently to permit passage of the object.

D. The stiffening tube may protect the mucosa from injury.

(Page 505)

11. GASTRODUODENAL FISTULA:

A. May connect the gastric lesser curvature to the first portion of the duodenum, or the greater curvature to the third or fourth portions, or be pyloroduodenal forming a double-barreled pylorus.

B. Pyloroduodenal fistula is found predominantly in young adults.

C. It is rarely associated with active ulcer diseases.

D. It is a congenital malformation.

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12. MULTIPLE LIVER ABSCESSES:

A. Are more commonly due to appendicitis than to cholangitis.

B. May follow suppurative pylephlebitis.

C. Portal vein thrombosis due to pylephlebitis can always be demonstrated by celiac arterial portography.

D. The portal vein may be entered during attempted percutaneous transhepatic cholangiography.

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13. ELECTROCOAGULATION OF BLEEDING UPPER GASTROINTESTINAL LESIONS:

A. Endoscopic monopolar electrocoagulation has had the widest clinical use of all the coagulation modalities in the U.S.A.

B. Active bleeding can be arrested in most or all cases.

C. The incidence of rebleeding after one treatment is approximately 10%.

D. Surgery can be avoided or performed electively rather than as an emergency in most cases.

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14. RECURRENT ABDOMINAL PAIN IN CHILDREN:

A. This is a common syndrome affecting up to 15% of children.

B. An organic cause can be found in over 75% of cases.

C. Annular pancreas is not an infrequent cause of neonatal upper intestinal obstruction.

D. Annular pancreas may cause recurrent abdominal pain without apparent obstruction in childhood.

(Page 522)

15. CECAL VOLVULUS:

A. Involves only the cecum and is usually counter-clockwise.

B. The rotated cecum is always displaced out of the right lower quadrant.

C. The dilated air-filled cecum seen on plain abdominal films shows no haustra.

D. A contrast enema always demonstrates twisted mucosal folds at the obstruction point adjacent to the dilated loop.

(Page 524)

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# BOOK REVIEWS FOR GASTROENTEROLOGISTS

**Clinical Pharmacology: Basic Principles in Therapeutics, 2nd edition: edited by Kenneth L. Melmon, M.D. and Howard F. Morrelli, M.D. 1,146 pages, illustrated. Macmillan Publishing Co., Inc., New York, NY, 1978. Price $25.00, cloth; $19.95, paperback.**

This is the second edition of this excellent book, edited by Drs. Melmon and Morrelli, both Professors of Medicine and Pharmacology at the University of California School of Medicine in San Francisco. The contributors to the sections dealing with Hepatology and Gastroenterology are Drs. James Boyer (Hepatology) and Irwin Rosenberg and Charles Winans—all from the University of Chicago and all well known.

The book is divided into three units: the first dealing with principles of drug administration including pharmacokynetics; the second dealing with pathophysiology of disease and pharmacologic considerations in drug administration (this is the most specific part of the text); the third unit deals with the recognition and evaluation of effects of drug administration. This latter part even includes a section on the economics of drug use.

The book is printed in double columns and is over one thousand pages long. Bibliographies are organized alphabetically, are quite complete and extend into the mid 1970's. Still, like most text books, this—the second edition—*Clinical Pharmacology*, is not a substitue for keeping abreast by reading articles in journals dealing with modern therapy.

The book, in a paperback form, is indeed a bargain. I would recommend it being purchased by House Staff Officers in training in Medicine and medical subspecialties as well as in Family Practice and for trainees and practitioners of emergency medical care. It is a text that should be purchased by every medical school and major hospital library.

WALTER HARVEY JACOBS, M.D., F.A.C.G.

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**Surgical Endocrinology: Clinical Syndromes: edited by Stanley R. Friesen, M.D., 430 pages, illustrated. J. B. Lippincott Company, Philadelphia, PA, 1978. Price $27.00.**

This is a highly impressive book by a prominent editor and 28 outstanding contributors. There is no comparable text in the North American surgical literature.

The writing is up-to-date, elegant, precise and clear; the handsome illustrations and diagrams augment the facile reading.

The care with which each chapter was prepared and the editorial integration have yielded a textbook of the highest clinical and scientific standards.

The wealth of information in Friesen's *Surgical Endocrinology* will assure the book's prominence in a rapidly advancing surgical specialty. Surgeons, endocrinologists and medical students will find the book most valuable.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

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**Peripheral Circulation: edited by Paul C. Johnson, 369 pages, illustrated. John Wiley & Sons, Inc., Somerset, NJ 1978. Price $29.95.**

This well structured and handsomely illustrated book, edited by Paul C. Johnson of Tucson, AZ, is co-authored by 12 prominent vascular physiologists from the United States, Sweden and Denmark.

A wealth of information is contained in the chapters on Blood Vessel Mechanics, Hemodynamics, Peripheral Circulatory Control, Capillary Exchange and of the vascular physiology in the peripheral (target) organs.

This is a valuable up-to-date source of information for vascular physiologists and clinicians.

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**Tropical Medicine and Parasitology: Classic Investigations, Vol. 1 & Vol. 2: edited by B. H. Kean, M.D., Kenneth E. Mott, M.D. and Adair J. Russell. 677 pages, illustrated. Cornell University Press, Ithaca, NY, 1978. Price $50.00.**

Dr. Kean and co-editors have put together a very interesting compilation of classical papers in parasitology accompanied by biographical sketches of their authors. I would recommend the two volumes only to those interested in the history of medicine as well as those searching for original source material not readily obtainable in this area.

DAVID A. DREILING, M.D., F.A.C.G.

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**Food Allergy: by Frederic Speer M.D. 165 pages, illustrated. PSG Publishing Company, Inc., Littleton, MA, 1978, Price $16.00.**

It would be better to give this book the title "Adverse Reactions to Foods" rather than "Food Allergy". Dr. Speer is a wise, experienced, respected clinician and his book is a compendium of adverse reactions to ingested foods, rather than allergic reactions alone.

Much of the information is anecdotal but it is interesting. Unfortunately, too many didactic statements are made, such as: "Every case of ulcerative colitis or suspected ulcerative colitis should have an allergic workup . . ."

This book makes interesting reading for practitioners of the art of Gastroenterology who may digest its contents with the wisdom from experience. I would not recommend it for trainees.

WALTER HARVEY JACOBS, M.D., F.A.C.G.

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**Hepatotoxicity: The Adverse Effects of Drugs and other Chemicals on the Liver: by Hyman J. Zimmerman, M.D. 597 pages, illustrated. Appleton-Century-Crofts, New York, NY, 1978. Price $48.50.**

This is a timely valuable book with data and implications far beyond hepatology, gastroenterology and even general medicine. The subtitle, *The Adverse Effects of Drugs and Other Chemicals on the Liver* really could be expanded to the Adverse Effects of the Liver on Drugs and Other Chemicals.

The text is divided into four sections. The first, General Considerations, deals with normal and abnormal hepatic metabolism, the spectrum and mechanisms of hepatic toxicity, pathophysiology and most important the relationship between hepatic and chemical carcinogenesis.

Section 2 covers Experimental Hepatotoxicity and deals with important specific liver poisons. Section 3 is comprised of Environmental and Occupation Problems and Section 4 presents a comprehensive review of Drug Induced Hepatic Injury.

The text is concise and the style is interesting. A book worthwhile for one's library.

DAVID A. DREILING, M.D., F.A.C.G.

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# Postgraduate Gastroenterology

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**21-27 October 1979**

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IN THE ANXIOUS ULCER PATIENT

# THESE PARAMETERS MAY BE IMPROVING...

X-rays and gastroscopy show a marked reduction in crater size. Maximal acid output and basal acid output have decreased to near-normal levels. There is no occult blood in stools.

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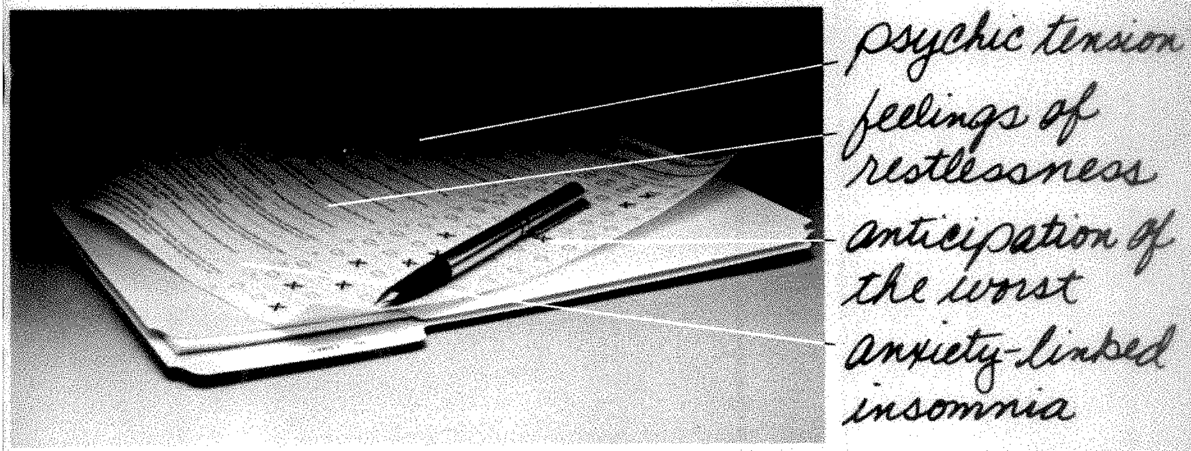
# BUT THESE MAY NOT.

All signs indicate that his duodenal ulcer is responding to medication and is healing "on schedule." But despite your reassurances, the patient remains excessively tense and apprehensive, continues to brood about minor G.I. symptoms, has difficulty following his prescribed regimen.

In such cases, adjunctive Valium (diazepam) can be distinctly helpful. Valium works promptly—often with initial calming in hours and more sustained, decisive anxiety relief in a matter of days. Before the week is out, then, the patient treated with Valium should report that he feels considerably more relaxed—and thus less hyperreactive—than before. Less troubled by "night-time" psychic tension, he also should be finding it easier to fall asleep.

Valium is, of course, used with most classes of primary medications, including $H_2$-receptor antagonists, anticholinergics and antacids. It is available in 3 scored-tablet strengths, simplifying dosage titration to meet patients' changing needs. And—a particularly important advantage—oral Valium is well tolerated by most patients. Although drowsiness, ataxia and fatigue are sometimes encountered, these and more serious side effects are rarely a problem. Patients should be cautioned against driving or drinking alcohol while on Valium (diazepam) therapy and should be encouraged to adhere to the prescribed dosage regimen or discuss any needed adjustment with you. When tension and anxiety have been adequately reduced, Valium therapy can be discontinued.



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**Before prescribing, please consult complete product information, a summary of which follows:**
**Indications:** Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).
The effectiveness of Valium (diazepam) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
**Contraindicated:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.
**Dosage:** Individualize for maximum beneficial effect. *Adults.* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
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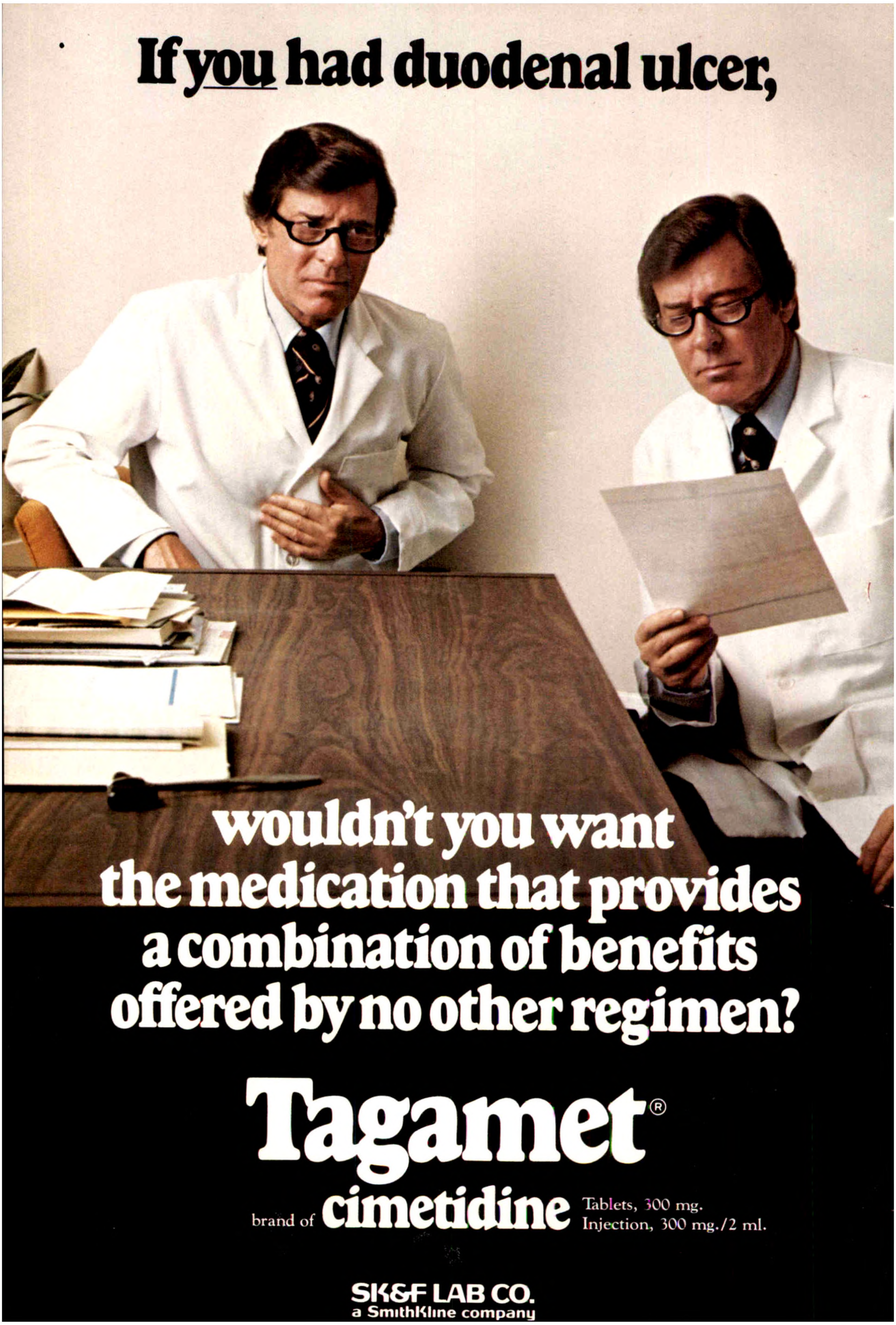
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**Dosage in Duodenal Ulcer**

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

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**Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.**

**Indications:** 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

**Contraindications:** There are no known contraindications to the use of 'Tagamet'.

**Precautions:** In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Potentiation of warfarin-type anticoagulants has been observed with concomitant 'Tagamet' administration. For this reason, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when these drugs are administered concomitantly.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

**Adverse Reactions:** Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

**How Supplied: Pale Green Tablets:** 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

**Injection:** 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials, in packages of 10.

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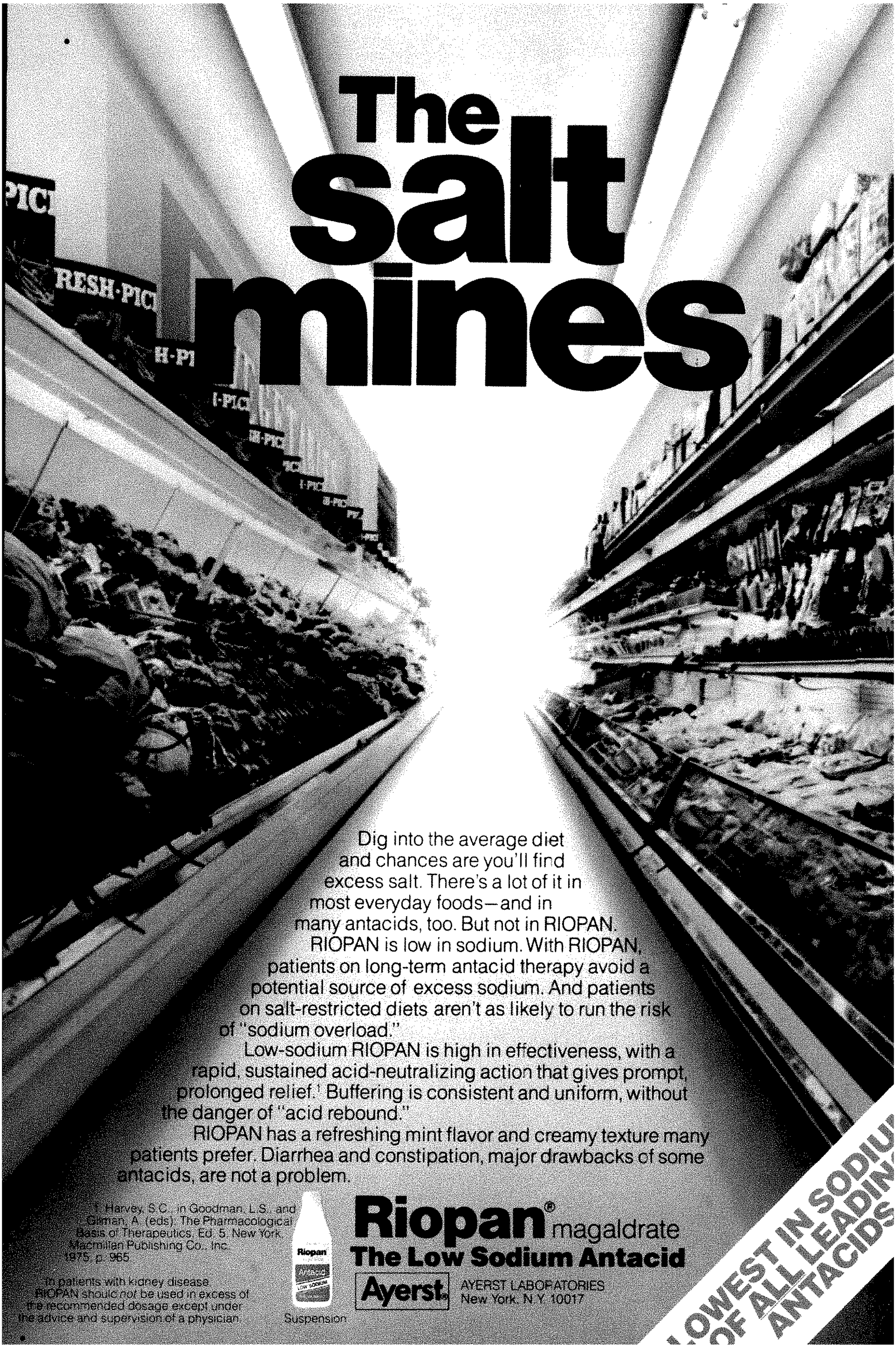

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[1] Harvey, S.C., in Goodman, L.S., and Gilman, A. (eds): The Pharmacological Basis of Therapeutics, Ed. 5. New York, Macmillan Publishing Co., Inc. 1975, p. 965.

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*The Pioneer Journal of Clinical Gastroenterology, Proctology and Allied Subjects in the United States and Canada*

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3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

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4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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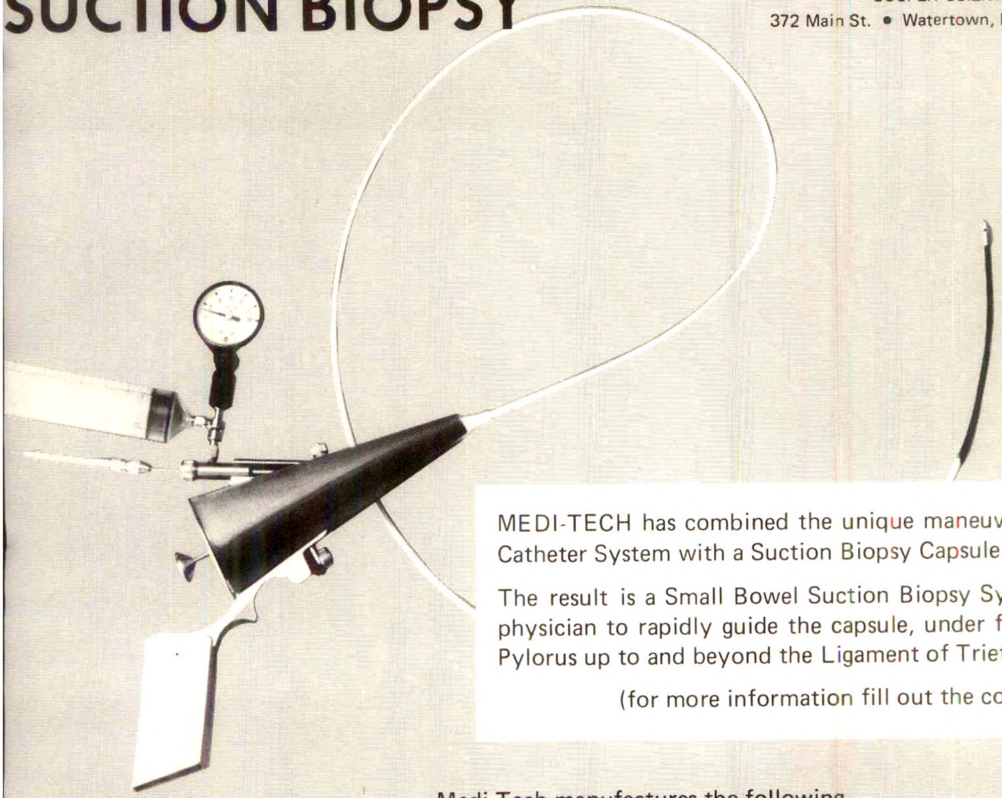

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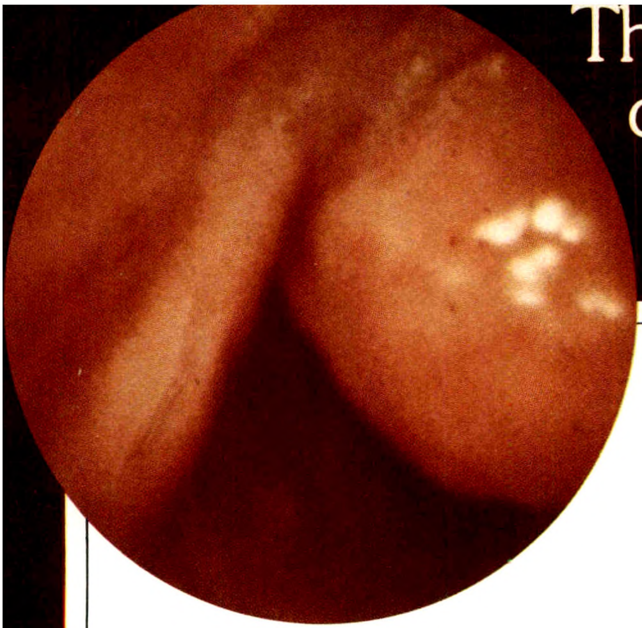

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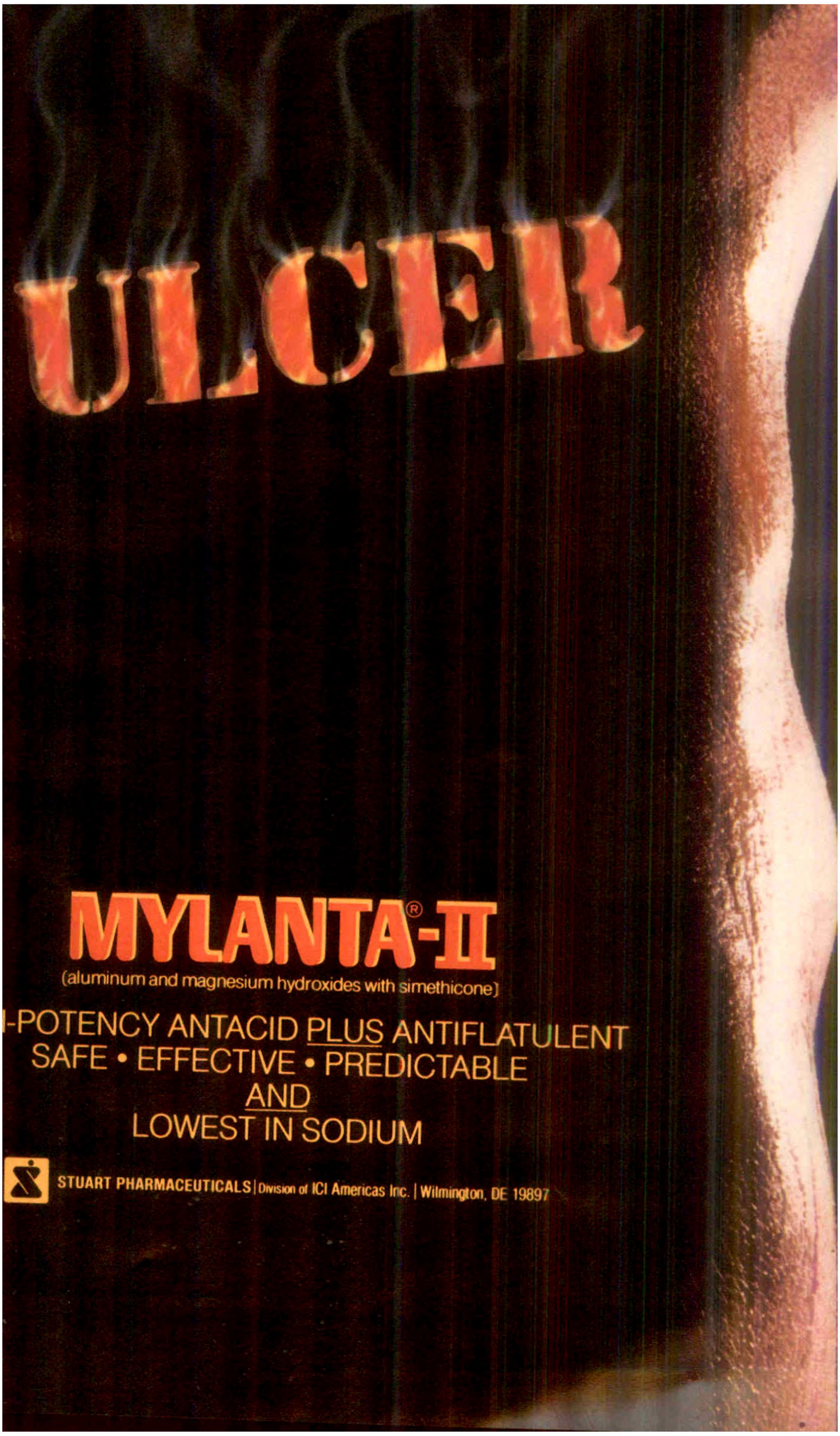

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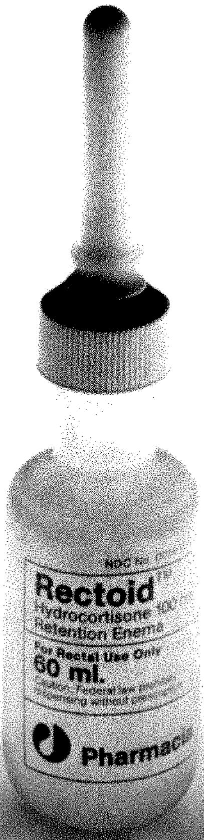

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Elevation of blood pressure, salt and water retention and increased excretion of potassium, requiring dietary restrictions and supplementation, may occur. All corticosteroids increase calcium excretion. *Immunization procedures, especially against smallpox, should not be undertaken in patients receiving corticosteroids, because of the possible hazard of neurological complications and lack of antibody response.* Close observation and chemoprophylaxis are indicated in patients with latent tuberculosis or tuberculin reactivity.
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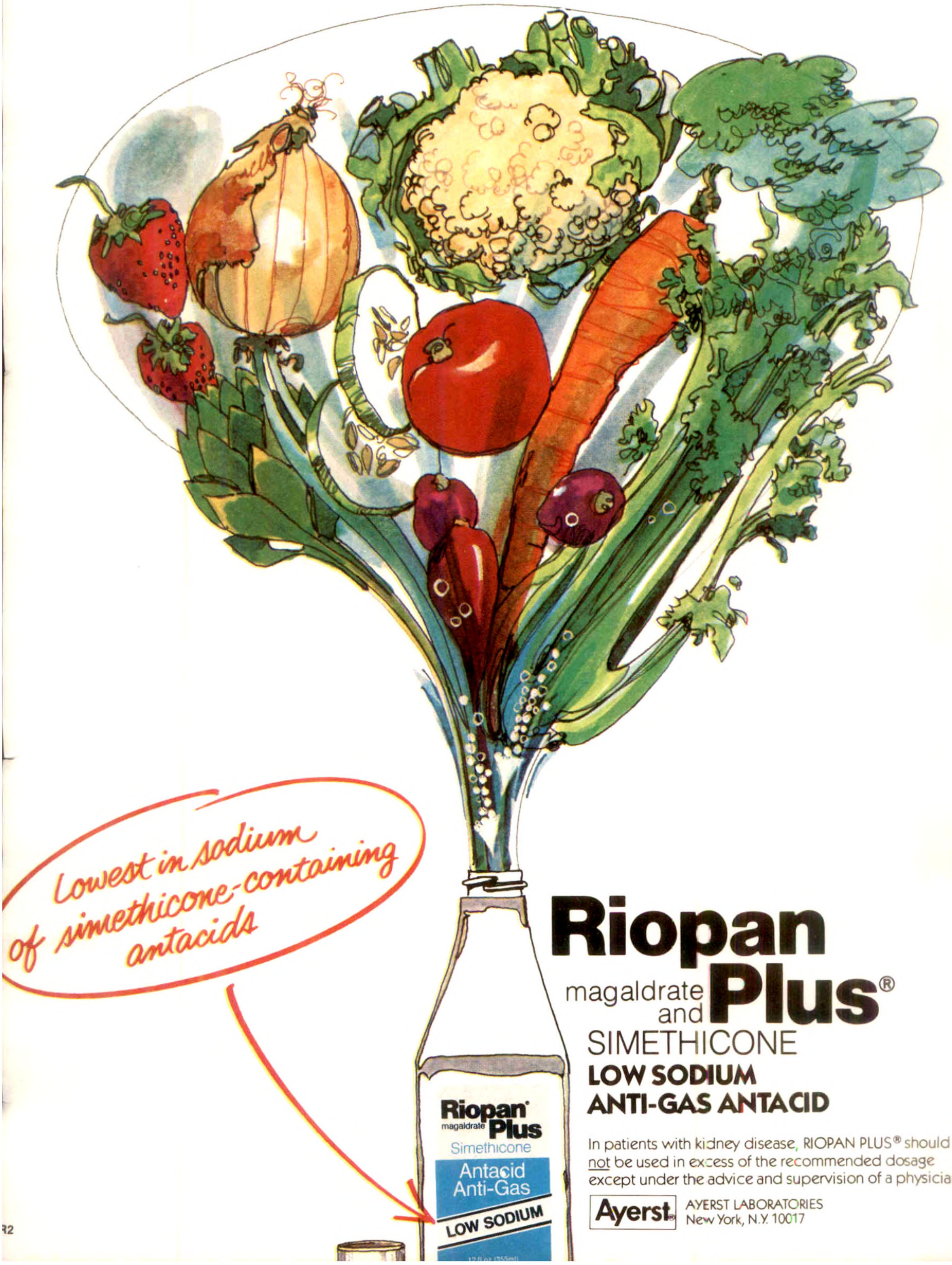

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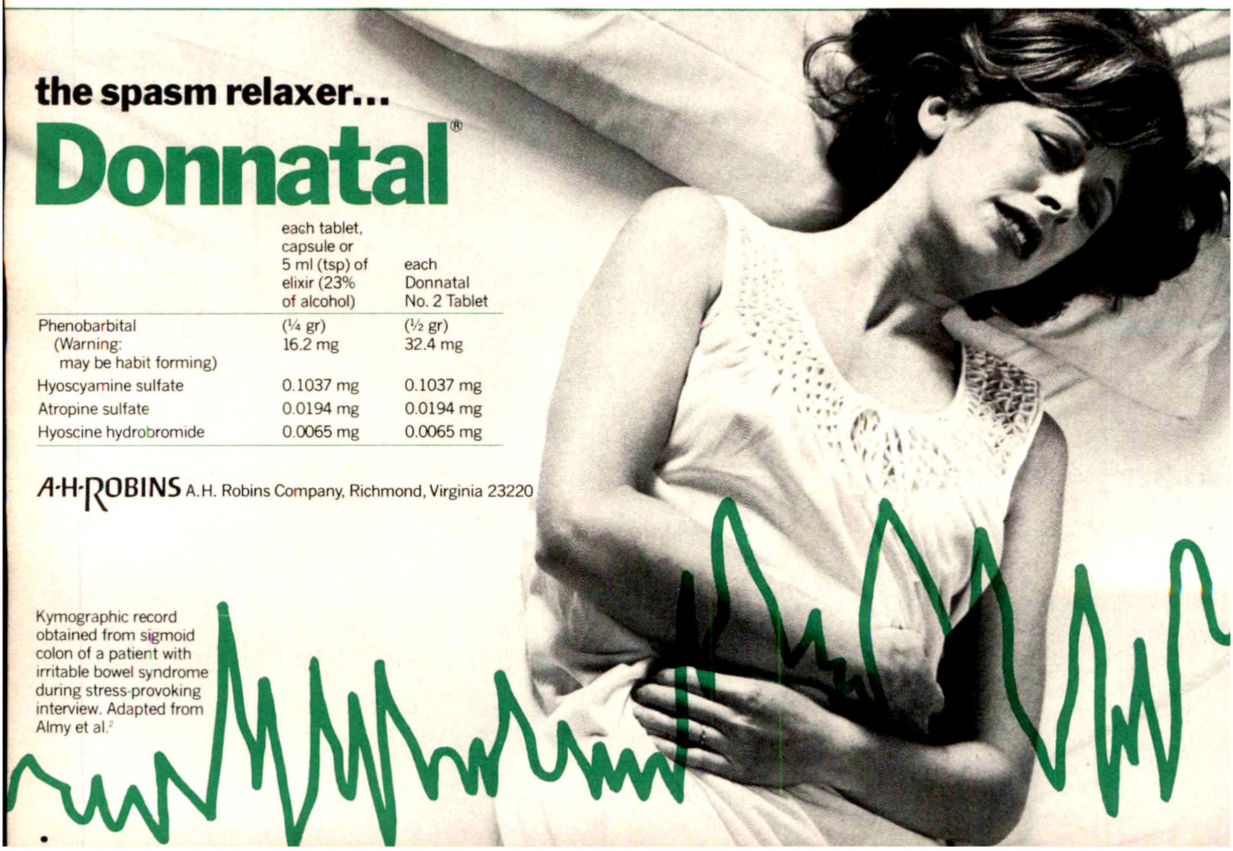

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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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VOLUME 71 JUNE, 1979 NUMBER 6

# Does Hyperamylasemia in the Drunken Alcoholic Signify Pancreatitis?*

J. EDWARD BERK, M.D., F.A.C.G.†
LOUIS FRIDHANDLER, Ph.D.‡
Orange, CA
and
SIDNEY F. WEBB, M.D.**
Las Cruces, NM

Amylase activity was assayed in the serum and urine of a series of unselected patients with acute alcohol intoxication to determine the frequency of elevated levels and the isoenzyme pattern in this condition. Hyperamylasemia was found in 16 (9.2%) of 174 inebriated patients. Isoamylase analysis disclosed that the rise in amylase activity in these 16 patients was due to a dominant increase in the salivary (S) form in seven, in the pancreatic (P) form in six and in both forms in one. Neither form exceeded the upper limit of normal in two. The same predominance of S-type over P-type elevation was found regardless of the level of total amylase activity in 82 patients in whom isoamylase analysis was made. Examination of urine for the relative amounts of total amylase to creatinine (110 patients), and the relative amounts of each of the principal isoamylases to creatinine (67 patients), gave findings paralleling those in the serum. Only one of 14 hyperamylasemic patients in whom the amylase clearance/creatinine clearance ratio was determined showed an elevated ratio. It is concluded: 1. hyperamylasemia and hyperamylasuria occur fairly often during episodes of acute alcohol intoxication and 2. rise in amylase activity in the intoxicated alcoholic does not in itself necessarily denote pancreatic damage as reflected in the fact that the rise is many times due to an increase in S-type rather than pancreatic-specific P-type isoamylase.

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From the Division of Gastroenterology, College of Medicine, University of California, Irvine.

Supported by a grant from the John A. Hartford Foundation, Inc. Partially supported also by a grant from the Bockus International Society of Gastroenterology.

[*] Read before the 43rd Annual Convention of the American College of Gastroenterology, Denver, Colo., 25, 26, 27 September 1978 (Preliminary data presented at Scientific Meeting of the Bockus International Society of Gastroenterology, London, England, 14 June, 1978).

[†] Professor of Medicine and Head, Division of Gastroenterology, University of California, Irvine.

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[**] University of California, Irvine, Medical Center.

## INTRODUCTION

The requirement that inebriated persons who come under custody of the police be brought to a hospital has greatly increased the number of patients with acute alcoholism seen in Emergency Rooms. Should any acutely intoxicated patient describe symptoms referable to the abdomen, particularly pain, the probability is great that amylase activity in the serum and/or urine will be measured. If the activity of this enzyme should be found to be increased, it is equally probable that this will be construed as indicative of acute pancreatitis complicating the alcoholic state and prompt such a working diagnosis.

Observations have been made by us and by others of the relative amounts of the two principal isoenzymes of amylase (pancreatic or "P"-type, and salivary or "S"-type) in a variety of clinical conditions attended by hyperamylasemia.[1, 2] These have shown that in many instances the amylase rise was most likely due to factors other than pancreatic disease, as evidenced by failure for the isoamylase form that specifically emanates from the pancreas (P-type)[3] to be elevated above its top normal limit. These observations prompted us to examine the total amylase levels and the isoamylase composition in the serum and urine of a series of patients with acute alcohol intoxication. Our purpose was two-fold: 1. to assess the frequency of occurrence of hyperamylasemia and hyperamylasuria in acute alcoholism, without regard to the presence or absence of abdominal symptoms and 2. to determine whether hyperamylasemia and/or hyperamylasuria associated with acute alcohol intoxication are by themselves indicative of acute pancreatitis.

## MATERIAL AND METHODS

Serum samples were obtained from 174 patients with acute alcohol intoxication seen in the Emergency Room of the University of California, Irvine, Medical Center. Urine samples were additionally obtained in 110 of these patients.

Total amylase activity was determined in each of the serum samples by means of an automated saccharogenic method[4] as modified.[5] Isoamylase analysis was additionally made in 82 of the serum samples and 67 of the urine specimens by a chromatographic method[3] subsequently modified.[5] From the data obtained by this method of study, it is possible to calculate how much of the total amylase activity is composed of the isoamylase of pancreatic origin (P-type)[3] and how much of the form that arises from salivary tissue as well as various other sources (S-type).[1, 2, 6]

Total amylase activity and the ratio of total amylase to creatinine (Uam/Ucr)[1, 5] were determined in all of the 110 urine specimens. The ratio of P-type isoamylase to creatinine (Upam/Ucr) and of S-type isoamylase to creatinine (Usam/Ucr), were also independently determined in 67 of these samples.[5] The amylase clearance/creatinine clearance ratio (Cam/Ccr)[7] was estimated in 107 patients from whom both serum and urine specimens were obtained.

## RESULTS

Values for total serum amylase activity in excess of the established upper limit of normal for the technic employed (171 mg. glucose/dl.) were found in 16 (9.2%) of the 174 patients whose sera were examined (Table I). The highest value in the 16 patients with abnormally elevated total serum amylase levels was 512 mg. glucose/dl.

Of the 82 patients whose sera were analyzed for isoamylase distribution, P-type isoamylase alone was found to be elevated above the upper limit of normal for this component (96 mg. glucose/dl.)[5] in eight

TABLE I

Frequency of Hyperamylasemia in Acute Alcoholism

| Patients | Hyperamylasemia* |
|---|---|
| 174 | 16 (9.2%) |

*Serum amylase > 171 mg. glucose/dl.

TABLE II

Isoamylase Elevations in Acute Alcoholism

| Patients | Isoamylase elevated | | |
|---|---|---|---|
| | P | S | Both |
| 82 | 8(9.8%) | 9(11%) | 1(1.2%) |

patients (9.8%); S-type alone was above its upper normal limit (119 mg. glucose/dl.)[5] in nine patients (11%) and both P- and S-types were abnormally elevated in one patient (1.2%) (Table II). In the 16 patients whose total serum amylase activity was increased above the upper limit of normal, P-type isoamylase alone was elevated in six (37.5%), S-type isoamylase alone in seven (43.8%), both P- and S-types in one (6.2%), and neither P- nor S-type exceeded their respective upper limits of normal in two (12.5%) (Table III). The highest value for P-type isoamylase was 345 mg. glucose/dl.; the highest value found for S-type isoamylase was 435 mg. glucose/dl.

Uam/Ucr was increased above the established upper limit of normal (7.4%)[5] in 11 (10%) of the 110 inebriated patients in whom this ratio was determined (Table IV). The same ratio in the urine for P-type isoamylase (Upam/Ucr) exceeded the upper limit of normal for this measurement (5.7%)[5] in three (4.5%) of the 67 patients in whom this parameter was determined (Table IV). In contrast, the ratio for S-type isoamylase (Usam/Ucr) was above the upper limit of normal for this measurement (3.7%)[5] in eight (11.9%) of the 67 patients who were examined (Table IV).

Cam/Ccr was elevated in 31 (29%) of the 107 subjects in whom this ratio was determined (Table V). In the 14 patients within this group who displayed hyperamylasemia, however, only one (7.1%) had an elevated Cam/Ccr ratio.

## Comment

The observations that have been reported by various investigators with respect to the behavior of amylase in patients considered to be alcoholic have not been uniform and altogether in accord. Christiansen[8] reported in 1936 that six of 10 chronic alcoholic patients whom he studied displayed elevations in serum amylase. Two of these patients were followed longitudinally; their amylase values were found to vary widely and were most often normal. In 1943, Siegel and Krautman[9] observed that serum amylase is often decreased, while urine amylase is often increased in the chronic alcoholic patient examined in a state of acute alcohol intoxication. Carter[10] emphasized in 1945 that serum amylase was frequently elevated in chronic alcoholics with severe abdominal symptoms. A more systematic study done by Domzalski and Wedge,[11] reported in 1948, was prompted by the possibility that hyperamylasemia might reveal subclinical pancreatitis. They found elevated serum amylase levels in 12 of 50 alcoholic patients as compared with only one of 50 control subjects.

Myhre and Nesbitt[12] reported in 1949 that they could not find any significant elevation of activity of amylase in the serum of normal subjects after the ingestion of alcohol. Culotta and Howard,[13] in 1954, described measurements made by them of plasma amylase in 51 patients with acute alcoholism; while six of the patients showed amylase levels in the plasma higher than normal subjects, the elevation was marked

TABLE III

ISOAMYLASE ELEVATIONS IN PATIENTS WITH ACUTE ALCOHOLISM AND HYPERAMYLASEMIA[*]

| | Isoamylase > Top normal | | | |
|---|---|---|---|---|
| Hyperamylasemic patients | P | S | Both | Neither |
| 16 | 6 (37.5%) | 7 (43.8%) | 1 (6.2%) | 2 (12.5%) |

[*] Serum amylase > 171 mg. glucose/dl.

in only two of the patients. Further, none of the patients presented physical findings suggestive of pancreatitis. Nossel[14] made note in 1955 of a study carried out on four patients who underwent cholecystectomy for cholelithiasis and chronic cholecystitis and in whom a T-tube drain had been left in the common bile duct. None of the patients had a history of pancreatitis. After ingestion of 30 ml. of whiskey, the common bile duct pressure rose within 20 minutes. Serum amylase, however, was unchanged at two and a half and three and a half hours after the alcohol had been taken. Fisher, et al[15] reported in 1976 that serum amylase was unaffected in 20 normal subjects studied by them up to 36 hours after acute alcohol intoxication. Skude and Wadstein[16] reported in 1977 on studies that they had conducted of serum amylase in 182 men who were considered to be chronic alcoholics. A few displayed high values for pancreatic amylase even though pancreatic disease had not been diagnosed clinically. In 6% of this group, total serum amylase values were low, while 20% were found by electrophoretic isoamylase analysis to have decreased activity in the serum of pancreatic isoamylase.

Our observations indicate that elevated amylase activity occurs with surprising frequency in unselected patients with acute alcohol intoxication. Also noted and of particular interest, was that when there was a rise above the upper limit of normal in either of the two major isoamylase forms, the rise was more often found in the S-type than in the more specific pancreatic P-type isoamylase.

Our findings in the urine of the patients we studied essentially paralleled those in the serum. Thus, the ratio of S-type isoamylase to creatinine in the urine, a measure of the relative amount of isoamylase present, was elevated more often than the ratio of the P-type isoamylase to creatinine in the urine.

The occurrence of an elevated Cam/Ccr ratio in 29% of the 107 acutely intoxicated patients in whom this determination was made would suggest that a sizable proportion of these inebriated persons did indeed have some pancreatic alteration. When, however, only those acutely intoxicated alcoholics who exhibited hyperamylasemia are considered, the results of the Cam/Ccr ratio determinations are entirely different. Thus, of 14 patients who displayed hyperamylasemia, only one (7.1%) had an elevated Cam/Ccr ratio. This is to be emphasized because Warshaw and Fuller,[7] in their initial report on the value of the Cam/Ccr ratio in the diagnosis of acute pancreatitis, stressed that the determination was of pertinence in differential diagnosis of patients who displayed *hyperamylasemia*. The Cam/Ccr ratio appears to lack the same degree of specificity or reliability in the absence of hyperamylasemia.

The frequency of occurrence of an elevated S-type isoamylase in the group of

TABLE IV

RATIO OF AMYLASE TO CREATININE IN URINE OF PATIENTS WITH ACUTE ALCOHOLISM

| | Number patients | Elevated ratios |
|---|---|---|
| Total amylase | 110 | 11(10%)* |
| P-type isoamylase | 67 | 3(4.5%)** |
| S-type isoamylase | 67 | 8(11.9%)*** |

* > 7.4
** > 5.7
*** > 3.7

TABLE V

AMYLASE CLEARANCE/CREATININE CLEARANCE RATIOS IN PATIENTS WITH ACUTE ALCOHOLISM

| | Number patients | Elevated ratios* |
|---|---|---|
| All patients | 107 | 31(29%) |
| Hyperamylasemic patients | 14 | 1(7.1%) |

* > 4%

acutely intoxicated alcoholic patients that we studied is intriguing. The explanation for the rise in this form of amylase is not altogether clear and permits only speculation. The origin of serum S-type isoamylase is not entirely defined as yet. While there is evidence indicating that the salivary glands are a major source of this form of amylase,[17, 18] other tissues, including the lung[6] and various tumors,[19] have also been shown to be contributors of S-type isoamylase. Indeed, we have found a small amount of S-type amylase in extracts from the pancreas itself.[20]

Parotid swelling has been noted to be associated with alcoholism.[21, 22] Of related interest are the studies of Grimmel, et al[23] suggesting that secretin and pancreozymin may elevate salivary amylase concentration in man, and those of Henn, et al[24] suggesting that a rise in both serum S-type and P-type isoamylase may be induced by secretin infusion given intravenously. It is possible, therefore, that alcohol may provoke secretin release and the latter, in turn, may be responsible for S-type iosamylase elevation in the serum.

Further speculation with respect to the pathogenesis of the S-type isoamylase rise seen in some of the patients with acute alcoholism may extend to prostaglandin $E_1$. This interesting substance has been reported to reduce volume of pancreatic secretion and output of electrolytes and at the same time to stimulate enzyme elaboration in dogs.[25] In a study conducted by Lillie in rats,[26] prostaglandin $E_1$ appeared to increase plasma amylase through an effect on the parotid gland. Should prostaglandin release be effected by alcohol, it is conceivable that a rise in serum S-type isoamylase may follow through the operation of these mechanisms.

Whatever may be the explanation for the rise in S-type isoamylase, the data here presented indicate that elevated total amylase activity in the inebriated alcoholic does not in itself necessarily signify pancreatitis; in a surprisingly large percentage of instances, the elevated amylase level is due to an increase in S-type isoamylase rather than in the form considered to originate only from the pancreas (P-type). It is to be emphasized in this respect that it is neither implied nor should it be inferred from these data that failure to find increased levels of total amylase activity and/or an elevated P-type isoamylase in patients with acute alcohol intoxication excludes with certainty the existence of pancreatic edema or some other morphologic alteration of the pancreas. The observations indicate only that when there *is* a rise in total amylase activity, the rise in itself is not necessarily reflective of pancreatic derangement.

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# Diagnosis of Early Gastric Cancer*

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Early gastric cancer is being encountered with increasing frequency in Germany as well as Japan and elsewhere through greater awareness, selection of high risk patients and improved diagnostic methods. We consider endoscopy superior to radiology in the detection of early gastric cancer. Polypoid lesions of the stomach need endoscopic biopsy or removal for proper diagnosis. Gastric ulcers should be followed by endoscopy and guided biopsies until healing is complete. Adequate sampling of a suspected gastric lesion may require multiple biopsy specimens for accurate histological interpretation.

"Early gastric cancer" is a well known malignant disease described mainly in the Japanese literature. The Japanese Gastroenterological Endoscopy Society defined the condition in 1962 as carcinoma of the stomach whose invasion is limited to the mucosa and submucosa of three types: Type I—protruded; Type II—superficial; Type III—excavated.

Type II was further subdivided into Type IIa (elevated), Type IIb (flat) and Type IIc (depressed). This definition is accepted worldwide. When resected, early gastric cancer has an excellent prognosis with a five-year survival rate of 85-90%.[1]

Extended experience with this type of gastric cancer in Europe, especially in Germany, has shown that the disease is not confined to Japan or Japanese[2] but exists worldwide. One reason it is found in other areas less often than in Japan is the lack of extensive screening as is practiced in Japan.

Mass screening is not done in Germany. The detection rate has been increased, therefore, by selecting high risk patients and by improved diagnostic methods. Among the high risk factors are: 1. a family history of gastric cancer; 2. pernicious anemia; 3. Ménétrier's disease; 4. a resected stomach (about 15 years after operation); 5. gastric polyps and 6. gastric ulcer.

Of all the diagnostic methods available, endoscopy with guided biopsies is our first procedure. We consider endoscopy superior to radiology because it can be performed

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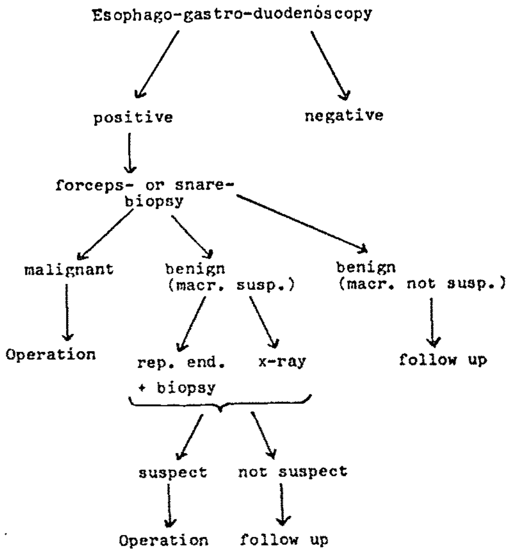

Fig. 1—Diagnostic approach.

quickly and safely and because suspected changes in the gastric mucosa can be readily sampled by various biopsy technics. Flat superficial lesions are easily identified endoscopically, because of subtle color changes between the normal and abnormal gastric mucosa.

Our diagnostic approach is outlined in Figure 1. Using this approach, the frequency of early cancer has increased in the past decade from 10-22% of all resected gastric cancers (Table I). This is short of the 20-40% detection rate reported by some Japanese authors[1, 3] but it compares favorably with the results of other European authors.[4, 5]

TABLE I

YEARLY INCIDENCE OF GASTRIC CANCER

| Year | Gastric cancer total | Early gastric cancer | Percentage |
|---|---|---|---|
| 1970 | 70 | 7 | 10 |
| 1971 | 67 | 4 | 6 |
| 1972 | 101 | 9 | 9 |
| 1973 | 83 | 10 | 12 |
| 1974 | 68 | 11 | 16 |
| 1975 | 38 | 7 | 18 |
| 1976 | 36 | 7 | 19 |
| 1977 | 33 | 6 | 18 |
| 1978 (1 Jan.- 30 June) | 18 | 4 | 22 |
| | 514 | 65 | 13 |

## PROTRUDED LESIONS

Polypoid or slightly elevated lesions (Types I and IIa) were encountered in 19 of our 65 cases (Fig. 2). In most cases, the surface of a protruded cancer is covered by carcinomatous mucosa. Exceptionally, it may represent a true gastric adenoma harboring a focal carcinoma. Only 4.8% of 706 benign gastric polyps were adenomatous in our series.[6]

In the majority of cases, forceps biopsy is sufficient to detect cancer in a protruded lesion of the stomach. Detection of a focal carcinoma in an adenoma, however, requires complete removal of the tumor by endoscopic polypectomy and serial section of the specimen. At the same time, polypectomy may be sufficient treatment, as in the case of a focal carcinoma occurring in a colonic adenoma (Fig. 3).

## FLAT LESIONS

The superiority of endoscopy over radiology is especially evident with Type IIb early gastric cancer. This type of lesion (four of our 65 cases) is flat and would not be expected to produce few radiological changes. On the other hand, endoscopy may detect changes in the color of the mucosa

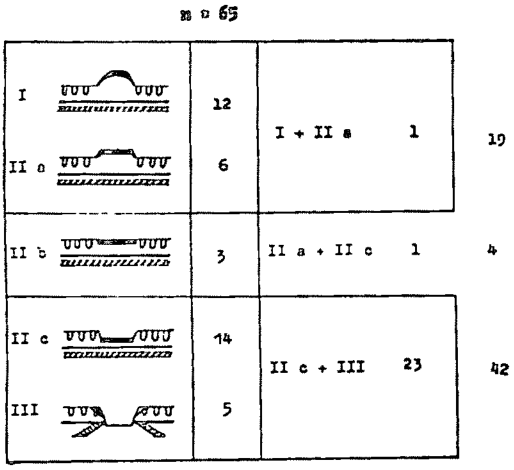

Fig. 2—Distribution of early gastric cancer.

forceps
snare-biopsy

Fig. 3—Diagnosis of cancer in a protruded lesion.

and small erosions in the carcinomatous mucosa. Since malignant lesions of the stomach may appear benign endoscopically,[7] we often biopsy gastric erosions and similar changes so as not to miss an early cancer. In our opinion the endoscopic impression should always be confirmed histologically.

## DEPRESSED LESIONS

In agreement with the data reported in the Japanese literature, Type IIc and Types IIc + III were the most common cancers in our material. This may be related to the fact that most of our patients were referred with established ulcer disease. Some 5% of macroscopically benign ulcers prove histologically to be malignant and are really peptic ulcerations within a carcinomatous mucosa, which tend to heal through covering of the crater by the carcinomatous mucosa.

At the first endoscopic examination, a gastric ulcer may appear histologically benign because of the limited extent of the malignant process. Therefore, we endoscope every ulcer-patient at three- to four-week intervals with biopsies from the ulcer until complete healing has occurred, both macroscopically and microscopically. Only then do we consider cancer as entirely excluded.

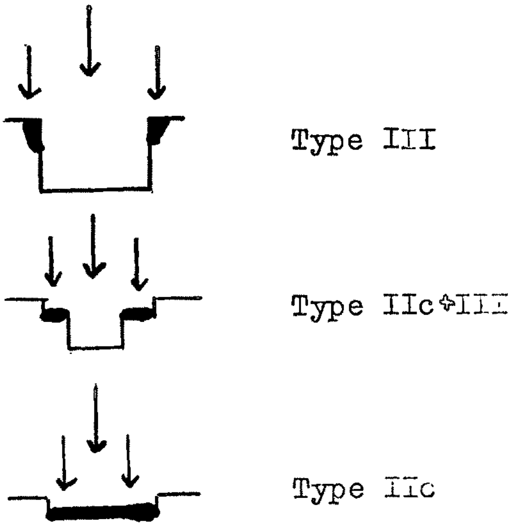

Fig. 4—Diagnosis of cancer in depressed lesions.

The necessity for the management described above is well demonstrated in our material (Table II). In only three cases did biopsies fail to reveal the cancer and in two of these three cases, the diagnosis was made by cytology. The third patient was suspected of having a Type IIc + III early gastric cancer and was operated upon without endoscopic follow-up. The protruded types, flat types and Type IIc were all diagnosed on the first biopsies, while four of 29 cases with Type III or Type IIc + III were diagnosed on the second biopsy and three others on the third examination.

The biopsies must always be taken from the margin of the ulcer or from the surrounding area (Fig. 4). At least five biopsies, preferably more, should be taken from the suspected lesion. Kasugai has clearly shown that the accuracy of detection

TABLE II

Accuracy of Biopsy Diagnosis in Early Gastric Cancer

| Type | No. | 1. biopsy pos. | 2. biopsy pos. | 3. biopsy pos. |
|---|---|---|---|---|
| I<br>IIa | 19 | 19 | | |
| IIb | 4 | 4 | | |
| IIc | 14 | 14 | | |
| III | 5 | 2 | 2 | |
| IIc + IIIc | 23 | 16 | 2 | 3 |
| Total | 65 | 55 | 4 | 3 |

In three cases cancer was not found by repeated biopsies.

TABLE III

Histological Cancer-types in Multiple Early Cancer Lesions

| | Total | Interstitial type | Diffuse type | Mixed n |
|---|---|---|---|---|
| Double early cancer | 12* | 9 | 1 | 1 |
| Early cancer + borderline lesion | 9 | 6 | 2 | 1 |
| Multicentric | 13 | 8 | 5 | – |
| Microscopically discontinuous | 35 | 10 | 23 | 2 |

(69 out of 270 cases of early gastric cancer = 24%)

* In one case of a double early cancer, both types were present.

increases with the number of biopsy specimens obtained.[8]

Two further aspects are worth emphasizing: first, early gastric cancer does not always occur as a single lesion. In Elster's series of 270 histologically examined early gastric cancers, 24% were multicentric (Table III). Thus, careful examination of the entire stomach harboring a suspected lesion is indicated. Second, 13% of Elster's cases showed a discontinuous pattern. Most of these cancers are differentiated adenocarcinoma and show cancer tissue interrupted by normal tissue. Multiple biopsies are again indicated.

## Conclusion

Through selection of high risk patients and improvement in diagnostic technics, the detection of early gastric cancer should increase in countries where endoscopy is readily available. Hopefully, increased detection will improve the overall survival rate of gastric cancer.

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# Effect of Monopolar Electrocoagulation on Esophagus, Stomach and Duodenum in Dogs

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The effects of electrocoagulation on the esophagus, stomach and duodenum of mongrel dogs were studied. A commercially available electrocoagulator unit and suction electrode were used. Various dial settings and duration times were used. The total number of sites electrocoagulated was 945; histologic section of each site was prepared. A dial setting of 7 and duration of 5 seconds was safe for the canine esophagus and duodenum; for the stomach it is a dial setting of 7 and duration of 3 seconds. This information will be useful in safe application of electrocoagulation to superficial bleeding lesions in the canine esophagus, stomach and duodenum.

Upper gastrointestinal bleeding is a common medical emergency. The mortality is significant and varies between 8 and 14% but may be as high as 50%.[1-4] Acute and chronic ulcerations in the esophagus, stomach and duodenum are the major causes of upper gastrointestinal hemorrhage;[5, 6] drug-induced acute erosive gastritis and stress ulcers are also important in this respect.[7-9] Now it is possible to coagulate bleeding gastrointestinal lesions by using flexible suction electrodes which can be passed via the fiberoptic endoscope.[10-17] This approach is particularly attractive in patients who are not fit for surgery. Electrocoagulation is not, however, always safe[18] and the amount of electric energy which can be safely delivered to a particular site needs to be determined. Some attempts have been made to determine the amount of energy delivered to the tissues.[19, 21] We used a commercially available electrocoagulation unit and suction electrode to study the effect of various dial settings and time duration on the canine esophagus, stomach and duodenum. The total number of sites electrocoagulated was 945; histologic section of each site was prepared. This information will be useful in safely employing electrocoagulation to stop bleeding from small superficial lesions in the esophagus, stomach and duodenum of dogs.

## MATERIALS AND METHODS

Male mongrel dogs weighing 15 kg. were fasted overnight and anesthetized with intravenous nembutal 30 mg./kg. The abdomen was opened by a ventral midline incision. Esophagus, stomach and duodenal bulb were opened and electrocoagulation of various sites was performed by lightly applying a suction electrode (Cameron-Miller 80-7035) using a coagulator unit (Cameron-Miller 80-7960). All the sites were electrocoagulated by the same oper-

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Supported by a grant from the Veterans Administration Medical Research Service.

TABLE I

EFFECT OF ELECTROCOAGULATION ON CANINE ESOPHAGUS, STOMACH AND DUODENUM

| | | Dial setting 5 | | | Dial setting 6 | | | Dial setting 7 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Duration | 1 sec. | 3 sec. | 5 sec. | 1 sec. | 3 sec. | 5 sec. | 1 sec. | 3 sec. | 5 sec. |
| Esophagus | | | | | | | | | | |
| Class A | | 35 | 30 | 25 | 35 | 29 | 24 | 32 | 27 | 22 |
| Class B | | 0 | 5 | 10 | 0 | 6 | 11 | 3 | 8 | 13 |
| Class C | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stomach | | | | | | | | | | |
| Class A | | 35 | 28 | 24 | 35 | 27 | 20 | 30 | 25 | 18 |
| Class B | | 0 | 7 | 10 | 0 | 8 | 8 | 5 | 10 | 7 |
| Class C | | 0 | 0 | 1 | 0 | 0 | 7 | 0 | 0 | 10 |
| Duodenal Bulb | | | | | | | | | | |
| Class A | | 35 | 30 | 24 | 35 | 28 | 24 | 35 | 29 | 21 |
| Class B | | 0 | 5 | 11 | 0 | 7 | 11 | 0 | 6 | 14 |
| Class C | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

ator. Various dial settings and duration were used. Dial settings of 5, 6 and 7 and duration of 1, 3 and 5 seconds were used. There were 35 sites for each dial setting and for each duration of application (Table I). The depth of tissue damage was classified as: A, if only mucosa was affected; B, if mucosa and submucosa were affected and C, if it was transmural.

## RESULTS

The results are summarized in Table I. There were no perforations with these dial settings and duration of application. Safe application was defined as the maximum energy and longest duration which would produce class A or class B change but not class C. According to this definition, safe current for canine esophagus and duodenum is a dial setting of 7 and duration of 5 seconds; for the stomach it is a dial setting of 7 and duration of 3 seconds. On histologic examination there was coagulative necrosis of tissues and congestion and coagulation of blood vessels (Figs. 1, 2 and 3).

## COMMENT

In this experiment we used monopolar electrocoagulation. The active electrode has a small diameter and the current is concentrated in a small area; a large electrode plate placed under the dog completed the electric circuit. Coagulating current has intermittent radio frequency wave form which causes tissue desiccation and hemostasis. Monopolar electrocoagulation should be differentiated from the bipolar method where coagulation occurs between two nearby electrodes.[22] As the coagulating current flows through the tissues near the electrode, it heats and desiccates the tissue to form a necrotic layer. Ideal coagulating current should have no cutting quality. Electrocoagulation is less effective on a wet surface compared to a dry surface because moisture increases the area of contact and reduces the current density. Tissue temperature in the region of active electrode rises and the region of coagulative necrosis is likely to become less sharply defined with increasing temperature and heating time.[23, 24]

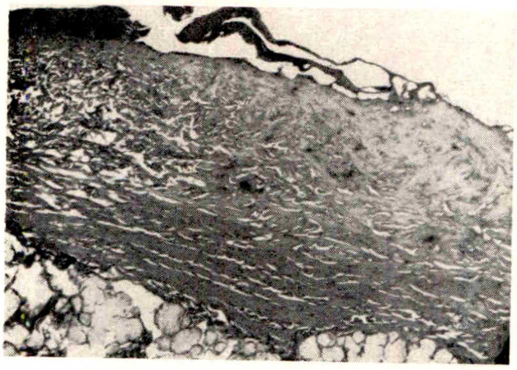

Fig. 1—Section of esophagus showing Class A change (Hematoxylin and eosin, original magnification x100).

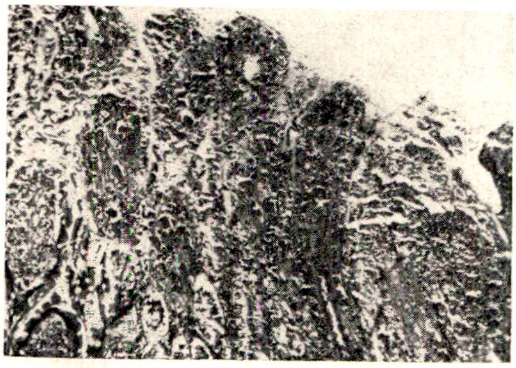

Fig. 3—Section of duodenum showing Class B change (Hematoxylin and eosin, original magnification x100).

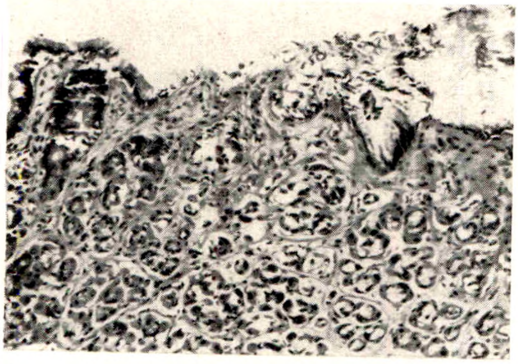

Fig. 2—Section of stomach showing Class A change (Hematoxylin and eosin, original magnification x250).

The histologic features of coagulative necrosis of mucosa, occlusion of mucosal and submucosal vessels seen in the present study have been observed by other workers.[11, 20] In our study esophagus and duodenum seemed to be more resistant than stomach to the effects of electrocoagulation; other workers had similar experience.[11] The reasons for this difference are not known but different water content of the mucosal cells may be a factor.

The major expected problem with electrocoagulation would seem to be full thickness burn and perforation. To avoid this possibility complex and expensive computer controlled electrocoagulation devices and laser beam application are being studied.[17, 25-33] All these efforts are aimed at accurately quantifying the amount of energy delivered to the tissues. It must be noted, however, that monopolar electrocoagulation of the rectum and rectosigmoid region via the proctosigmoidoscope has been performed for many years without serious problems. In the present study with the dial settings and duration of application used, there were no perforations. We plan to treat via fiberoptic endoscope superficial bleeding lesions in the canine esophagus, stomach and duodenum by using this method; the information obtained by the present study will be used to obtain the right dial setting and duration of application. This method utilizes a commercially available electrocoagulator and is inexpensive.

## ACKNOWLEDGMENT

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# Peritoneal Dialysis Clearance of Cimetidine

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Peritoneal dialysis clearance of cimetidine was determined in two patients undergoing peritoneal dialysis treatment. The peritoneal dialysis clearance of cimetidine was approximately 10 ml./min. under optimal dialyzing conditions. The average cimetidine to creatinine extraction ratio was 0.45, which represents significant peritoneal dialyzability. The amount of cimetidine removed, however, constituted only a small fraction of the total administered dose. Therefore, only minor dose adjustments may be necessary during peritoneal dialysis treatment.

## INTRODUCTION

Cimetidine, an $H_2$ receptor antagonist, has achieved widespread clinical use since its release by the FDA. It has been successfully used in the treatment of peptic ulcer disease,[1] Zollinger-Ellison syndrome,[2] esophagitis,[3] upper gastrointestinal bleeding,[4] and metabolic alkalosis induced by nasogastric drainage.[5]

With the recent introduction of chronic peritoneal dialysis as an alternative therapeutic modality in patients with end-stage renal disease and the continued use of acute peritoneal dialysis, the number of patients receiving peritoneal dialysis treatment has increased significantly. In view of the recognized hazards of conventional therapy for peptic disorders in patients with advanced renal failure, cimetidine will very likely become the treatment of choice in this patient population. To our knowledge, there are no available data on peritoneal dialysis clearance of cimetidine. Such information would be of clinical value in determining the proper dose adjustment of this drug in patients undergoing peritoneal dialysis. We, therefore, undertook an investigation to provide this information.

## PATIENTS AND METHODS

Petritoneal dialysis clearance studies were performed on two patients. Clinical data and indications for cimetidine therapy and peritoneal dialysis are summarized in Table I.

In Case 1, 300 mg. of cimetidine was given intravenously one hour prior to dialysis and repeated every 12 hours. In Case 2, oral cimetidine was started two days prior to peritoneal dialysis at a dose of 300 mg. every six hours and continued throughout the period of dialysis. Prior to the procedure the urinary bladder was emptied by straight catheterization. The area was prepared and draped in an aseptic manner. Local anesthesia was accomplished using 1% xylocaine solution. A small mid line longitudinal incision was made 3 cm. below the umbilicus using a #11 Bard-Parker blade. A peritoneal dialysis catheter (Stylo-Cath, Abbott Laboratories, North Chicago, IL) was then positioned in the left pelvic gutter. In Case 1, a standard 1.5% Dianeal solution was used containing dextrose

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TABLE I

CLINICAL DATA

| Case | Age and sex | Diagnoses and indications for dialysis | Indications for cimetidine administration | Cimetidine administration |
|---|---|---|---|---|
| 1 | 26 year old male | Acute intermittent porphyria, acute renal failure, fluid overload | Gastrointestinal bleeding | 300 mg. I.V. every 12 hours |
| 2 | 41 year old female | Alcoholic liver, disease, acute renal failure, severe lactic acidosis | Gastrointestinal bleeding | 300 mg. P.O. every 6 hours |

monohydrate, 15 gm./l.; sodium, 141 mEq/l.; calcium, 3.5 mEq/l.; magnesium, 1.5 mEq./l.; chloride, 101 mEq./l. and lactate, 35 mEq./l. A specialy prepared bicarbonate buffered solution containing dextrose monohydrate, 15 gm./l.; sodium, 140 mEq./l.; chloride, 110 mEq./l. and bicarbonate, 30 mEq./l. was used in Case 2 for treatment of concomitant lactic acidosis.

The dialysis solutions were warmed to 38° C prior to instillation into the peritoneal cavity. During the initial five exchanges, 500 units of sodium lipoheparin were added to each liter of dialysis solution to prevent catheter obstruction by fibrin clots. The volume of dialysate introduced into the peritoneal space with each exchange was 1.5 liters in Case 1, and 1 liter in Case 2. The dwell times were 15 and 5 minutes in Cases 1 and 2, respectively. Twenty milliliter aliquots of drained dialysate were collected at the end of each exchange and pooled in a larger container for cimetidine and creatinine assays during each collection period. Blood cimetidine and plasma creatinine levels were determined at the mid point of each collection period. Case 1 was dialyzed for approximately 20 hours with four individual collection periods. Case 2 was dialyzed for approximately 18 hours with six individual collection periods. Cimetidine assays were performed by the Smith, Kline and French Laboratories utilizing high pressure liquid chromatography as described by Randolph, et al[6] and checked twice for accuracy.

Peritoneal dialysis clearance of cimetidine was calculated using the standard formula $Cl = \frac{C_D \cdot Q_D}{C_B}$ where Cl represents clearance as ml./min., $C_D$ represents cimetidine concentration in dialysate outflow, $C_B$ represents cimetidine blood concentration (determined at the midpoint of each collection period) and $Q_D$ represents dialysate flow rate. $Q_D$ was determined by dividing the total dialysate outflow volume by the length of the effective dialysis time in each collection period. Effective dialysis time was considered to be the period between the initiation of inflow and the termination of outflow of the dialysate in each exchange. The collection periods consisted of a predetermined number of exchanges during which dialysate outflow samples were pooled.

## RESULTS

Dialysis data are summarized in Tables II and III for Cases 1 and 2, respectively. The average cimetidine blood level was 2.87 mcg./ml. (range 1.90-3.80

TABLE II

Dialysis and Clearance Data on Case 1

| Collections periods | Number of exchanges | Effective dialysis time min. | Volume in ml. | Volume out ml. | Blood cimetidine mcg./ml. | Dialysate cimetidine mcg./ml. | Peritoneal cimetidine clearance ml./min. | Peritoneal creatinine clearance ml./min. | Cimetidine to creatinine clearance ratio |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 6 | 212 | 9,000 | 9,550 | 1.90 | 0.5 | 11.85 | 30.03 | .39 |
| 2 | 6 | 283 | 9,000 | 9,150 | 3.20 | 0.9 | 9.09 | 21.13 | .43 |
| 3 | 6 | 385 | 9,000 | 9,000 | 3.80 | 1.2 | 7.38 | 14.89 | .50 |
| 4 | 6 | 275 | 9,000 | 9,200 | 2.60 | 0.9 | 11.58 | 20.91 | .55 |
| Average | | | | | 2.87 | 0.87 | 9.98 | 21.74 | .47 |

mcg./ml.) in Case 1 and 3.08 mcg./ml. (range 2.20-3.80 mcg./ml.) in Case 2. The average dialysate cimetidine concentrations were 0.87 and 0.43 mcg./ml. in Cases 1 and 2, respectively. The average blood/dialysate cimetidine ratio was 3.29 in Case 1 and 7.16 in Case 2. Peritoneal dialysis clearance of cimetidine averaged 9.98 ml./min. (range 7.38-11.85 ml./min.) in Case 1 and 3.06 ml./min. (range 1.39-4.44 ml./min.) in Case 2.

Peritoneal dialysis clearance of creatinine determined simultaneously averaged 21.74 and 7.06 ml./min. in Cases 1 and 2, respectively. The average cimetidine/creatinine extraction ratio was 0.47 in Case 1 and 0.43 in Case 2. The total cimetidine removed by peritoneal dialysis in 20 hours amounted to 32.3 mg. in Case 1. Only 8.8 mg. were removed during 18 hours of peritoneal dialysis in Case 2. The amount removed by peritoneal dialysis represented a small fraction of the total administered dose in each patient.

## COMMENT

With the advent of indwelling peritoneal catheters and automated peritoneal dialysate delivery systems, long-term peritoneal dialysis has gained widespread acceptance as a useful therapeutic modality in end-stage renal disease. Short term peritoneal dialysis is commonly used in the management of acute renal failure, reversible deterioration of stable chronic renal failure, end-stage renal failure awaiting maturation of vascular access for hemodialysis or the interim period before renal transplantation.

Since its release in the United States, cimetidine has received widespread clinical use in the treatment of peptic ulcer disease and other gastrointestinal disorders. Increased basal gastric acid secretion has been demonstrated in patients with renal failure,[7] predisposing such patients to a higher incidence of peptic disorders and upper gastrointestinal bleeding. Conventional treatment with magnesium containing antacids may be hazardous in advanced renal failure due to the risk of magnesium intoxication. Aluminum hydroxide is a weak antacid and when given in large amounts can cause constipation and phosphate depletion. Cimetidine represents an effective alternative in the treatment of these patients and may become the treatment of choice in such conditions.

Information on the peritoneal dialysis clearance of cimetidine has clinical importance as it relates to the possible need for dose adjustments in patients undergoing peritoneal dialysis. We have shown the clearance of cimetidine to range from 1.39-11.85 ml./min. in two patients treated with peritoneal dialysis. These values slightly overestimate the actual clearances in the presence of ultrafiltration. The degree of ultrafiltration and associated mass transfer were negligible, however, as evidenced by minimal negative dialysate balance (Tables II and III). The cimetidine clearance was approximately 45% of that of creatinine as evidenced by the cimetidine to creatinine extraction ratios of 0.47 and 0.43 in Cases 1 and 2, respectively. This represents a significant clearance for cimetidine. The amount removed constitutes, however, only a small fraction of the total dose administered during peritoneal dialysis. The hemodialyzability of cimetidine has been previously reported by Canavan, et al and Ma, et al.[8, 9] We have also undertaken studies to determine the hemodialysis clearance of cimetidine and found it to be approximately 40-75 ml./min. under various dialyzing conditions. As can be seen, hemodialysis is more efficient than peritoneal dialysis in removing cimetidine. The length of each hemodialysis treatment is usually quite short (4-6 hours), however, whereas, peritoneal dialysis is often con-

TABLE III

DIALYSIS AND CLEARANCE DATA ON CASE 2

| Collections periods | Number of exchanges | Effective dialysis time min. | Volume in ml. | Volume out ml. | Blood cimetidine mcg./ml. | Dialysate cimetidine mcg./ml. | Peritoneal cimetidine clearance ml./min. | Peritoneal creatinine clearance ml./min. | Cimetidine to creatinine clearance ratio |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 95 | 2,000 | 2,010 | 3.80 | .25 | 1.39 | 3.30 | .42 |
| 2 | 5 | 210 | 5,000 | 4,925 | 2.20 | .40 | 4.26 | 8.17 | .52 |
| 3 | 3 | 145 | 3,000 | 3,150 | 3.00 | .50 | 3.62 | 9.51 | .39 |
| 4 | 5 | 265 | 5,000 | 5,150 | 3.30 | .46 | 2.74 | 6.37 | .43 |
| 5 | 4 | 205 | 4,000 | 4,085 | 3.20 | .33 | 2.05 | 5.13 | .40 |
| 6 | 3 | 155 | 3,000 | 3,100 | 3.00 | .65 | 4.44 | 9.86 | .44 |
| Average | | | | | 3.08 | .43 | 3.06 | 7.06 | .43 |

tinued for 36-72 hours. Therefore, comparable amounts of cimetidine could be removed during peritoneal dialysis.

Peritoneal dialysis clearance of cimetidine in Case 1 was considerably higher than in Case 2. The latter, however, a patient with advanced hepatic cirrhosis, had severe lactic acidosis and profound hypotension during dialysis. We believe that the low cimetidine and creatinine clearances in this patient were primarily caused by poor perfusion of the peritoneal membranes due to the cardiovascular collapse. Furthermore, dialysate flow rate, another determinant of solute clearance, was lower in this patient (20.85 ml./min.) compared to Case 1 (31.95 ml./min.). Other factors which could have contributed to the observed disparity in clearances between the two patients include differences in the permeability of peritoneal membranes and the degree of drug-protein binding. With the available data, these mechanisms cannot be implicated with certainty, and the above-mentioned differences in peritoneal blood perfusion and dialysate flow rate seem to adequately explain the disparity. Peritoneal dialysis clearance of creatinine in Case 1 averaged 21.74 ml./min. representing an optimal peritoneal clearance as opposed to the corresponding value of 7.06 ml./min. in Case 2 which represents an unusually inefficient dialysis. We, therefore, feel the cimetidine peritoneal dialysis clearances under ordinary conditions should be about 10 ml./min. as found in Case 1. The cimetidine to creatinine extraction ratio of about 0.45 established in this report can serve to predict cimetidine clearances under various dialyzing conditions. Based on these results only minor dose adjustments may be necessary during peritoneal dialysis.

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# Gastric Irradiation of Peptic Ulcer*

## A 14-YEAR FOLLOW-UP

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We have employed gastric irradiation (1,500-2,000 rads) to treat 463 selected patients with peptic ulcer since 1963. Follow-up data are available on 422 (91%). Of these, 307 were male, 115 were female, ranging in age from 35-92 years, mean 63.2 years. Two hundred seven had duodenal ulcer; 82 had gastric ulcer and 174 had duodenal and gastric ulcer. Forty-eight patients (11.3%) died during the 14-year period of observation; none from ulcer, ulcer complications or gastric malignancy. Postmortem information was available on 14 patients and death-certificate information on 34. Forty-two patients, less than 10% of the population at risk, had recurrence of ulcer after treatment; 13 of these underwent surgery, with nine deaths occurring within one year postoperatively. The mean age of this recurrent group was 50.4 years.

Complete acid secretory studies were carried out on 463 patients before irradiation; 69 had repeat studies one to three years posttreatment; 60 had repeat studies three to 14 years posttreatment. Basal secretion tended to diminish with advanced age. In six patients studied posttreatment, serum gastrin levels did not change over a six-year period. Posttreatment response to histamine, pentagastrin and insulin resembled closely those reported after highly selective vagotomy.

We have been impressed with the favorable course of these patients as evidenced by marked decrease in antacid requirements, rare hospitalization and lack of complications. The total cost of medical care was definitely reduced. We consider gastric irradiation a definitive alternative in treating the ulcer patient who is elderly requiring ulcerogenic drugs for other disorders and who is a poor operative risk.

We initially employed gastric irradiation in the treatment of peptic ulcer in our hospital in 1960. In 1970, we reported a three-year follow-up on 33 patients.[1] From that experience, we concluded that gastric irradiation, in the dosage employed, produced an effect similar to that expected from vagotomy and pyloroplasty on acid volume and secretion. Furthermore, side-effects of vagotomy and pyloroplasty on intestinal motility and gastric emptying (not infrequently encountered following such surgery) are not reproduced by gastric irradiation. It seemed that gastric irradiation is a useful and safe method for treating peptic ulcer diathesis in poor risk pa-

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† Chairman, Executive Committee, Department of Medicine, Saint Joseph Hospital; Instructor, Johns Hopkins University School of Medicine.

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UNIVERSITY

tients for whom surgical management is deemed risky and medical management, inadequate.

The purpose of this report is to present data on 422 patients with peptic ulcer who were treated with gastric irradiation while having symptoms of active ulceration and followed for 14 years. The data stress the pattern of gastric secretion, careful clinical observations on all patients and the cost effectiveness of this form of treatment.

## Materials and Methods

Since 1960, 463 selected patients with peptic ulcer were treated with gastric irradiation. All patients included in this study had not responded to previous medical treatment, had evidence of complications or intractability of their ulcer diathesis and were considered candidates for more aggressive therapy. Several patients had had previous surgery for peptic ulcer. All patients had other medical conditions which were considered to greatly enhance their surgical risk. These included cardiac disease, pulmonary disease, hematologic bleeding diathesis, renal disease and collagen disease.

Of the 463 patients, follow-up data on 422 patients (91%) indicates that 307 were male, 115 female, ranging in age from 35-92 years; the mean age was 63.2 years. Duodenal ulcer was present in 207; gastric ulcer, in 82 and both duodenal and gastric ulcers were presented in 174.

## Gastric Irradiation

Gastric irradiation was administered as follows: We used cobalt and our technic conforms generally to that of Palmer[2] with the 250 kilovolt x-radiation machine. The stomach is outlined fluoroscopically with barium and the skin is marked. Two fields, one anterior and one posterior, each centered over the upper two-thirds of the stomach are outlined for therapy. It should be noted that the irradiation is not directed at the ulcer itself but at that portion of the stomach which contains the acid-secreting cells. Use of the two fields over the upper two-thirds of the stomach effectively cross fires this acid-secreting portion of the stomach. Approximately 100 rads are given through each port, in eight to ten treatments resulting in a total depth dose or stomach dose of 2,000 rads.

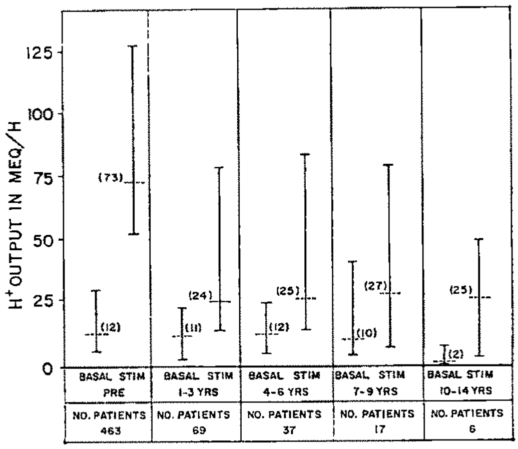

Fig. 1—Basal and stimulated acid aspirated before and at intervals up to 14 years after irradiation. Plotted as $H^+$ output in mEq./hr. mEq./hr.

## Procedure of Gastric Analysis

Gastric analysis was performed according to the method of Kay.[3] A 32 French rubber tube was placed into the antrum of the stomach under fluoroscopic control. The stomach contents were emptied and a basal 60-minute collection was obtained as four 15-minute samples. The patients were instructed to expectorate all saliva secreted during the test. Thirty minutes after the start of the basal collection, chlorpheniraminemaleate 30 mg. was injected intramuscularly. One hour after the start of the basal collection and 30 minutes after the in-

TABLE I

SIX PATIENTS MATCHED FOR AGE, SEX AND GASTRIC ACID SECRETION WHEN STUDIED WITH PENTAGASTRIN AND INSULIN STIMULATION

| | Preirradiation | Postirradiation |
|---|---|---|
| Basal | 11.0 $H^+$ mEq./hr. | 2 $H^+$ mEq./hr. |
| Pentagastrin | 78 $H^+$ mEq./hr. | 25 $H^+$ mEq./hr. |
| Insulin | 23 $H^+$ mEq./hr. | 5 $H^+$ mEq./hr. |

jection of the antihistamine, the patient received a subcutaneous injection of histamine acid phosphate in a dosage of 0.045 mg./kg. of body weight. The gastric secretions were collected for the ensuing one hour, again as four 15-minute samples. This latter one-hour collection was defined as maximal or stimulated acid output. An aliquot of each specimen of gastric juice was titrated to pH 7 electromatically with 0.1 N NaOH. The acid output was expressed as pH output mEq./hr. Results are for gastric analysis prior to, at one to three years, four to six years, seven to nine years and ten to 14 years, following gastric irradiation (Fig. 1). In six patients, acid secretion was studied prior to irradiation by insulin and pentagastrin stimulation. The baseline control and method of tube placement were the same as that described above. Blood sugar samples were obtained 15 and 30 minutes after the intravenous injection of insulin. The insulin dosage used varied from 0.1 U./kg.-0.8 U./kg. depending upon that amount of insulin required to reduce the level of glucose to below 50 mg.%.[4] In the case of pentagastrin,[5] 6 mcg./kg. were given subcutaneously. Gastric sampling was continued for one hour, as 15-minute aspirations. Results are shown in Table I.

Clinical follow-up included repeated individual evaluation in most patients by the authors. In some patients follow-up consisted of referring physician contact and a few patients were contacted by questionnaire. The usual follow-up consisted of interval history, physical examination, routine hematogram, SMA profile, stool and urinalysis. When clinically indicated x-ray and endoscopic procedures were utilized to assess symptoms of recurrent ulcer. Creatinine clearance was performed in 36 patients prior to and at varying intervals (four to six years) after irradiations. Six patients had the Schilling Test performed (six to nine years postradiation) and six patients had gastrin levels prior to and over a six-year period postirradiation.

## COST ANALYSIS

Twenty-seven patients had adequate records to compare medical care costs prior to and after radiation. As objective sources of this information, we used: 1. tax returns; 2. insurance payments records; 3.physicians' statements; 4. pharmacy statements; 5. hospital statements.

Diagnostic studies designated ulcer-related were included in the cost analysis: 1. gastrointestinal x-rays; 2. routine laboratory tests; 3. endoscopy.

Other cost-related items included: hospital days for primary peptic-ulcer-related problems, clinic visits for primary peptic-

TABLE II

TOTAL COST PRE- AND POSTIRRADIATION LISTED AS AVERAGE PER YEAR IN DOLLARS

| No. of patients | Years | Cost pre-irradiation (dollars) | Cost post-irradiation (dollars) |
|---|---|---|---|
| 4 | 1961-1965 | 387 | 75 |
| 9 | 1965-1969 | 633 | 184 |
| 8 | 1969-1973 | 1,017 | 305 |
| 6 | 1973-1976 | 1,129 | 297 |

TABLE III

NUMBER OF CLINIC VISITS PRE- AND POSTIRRADIATION FOR PEPTIC ULCER-RELATED PROBLEMS

| No. of patients | Years | No. of visits pre-irradiation | No. of visits post-irradiation |
|---|---|---|---|
| 4 | 1961-1965 | 22 | 5 |
| 9 | 1965-1969 | 18 | 4 |
| 8 | 1969-1973 | 15 | 4 |
| 6 | 1973-1976 | 19 | 6 |

ulcer complaints and drug-related costs (antacid, anticholinergics, sedation, analgesics.)

The cost analysis period included costs accumulated one year prior to irradiation treatment and for two years posttreatment (Tables II and III).

## RESULTS

Complete acid secretory studies were carried out on 463 patients prior to irradiation and data on them prior to treatment and posttreatment are shown in Figure 1. These results do not differ significantly from the first three-year observation in that the basal secretion tended to return to the preradiation level whereas the stimulated values remained lower. It should be pointed out, however, that with advancing age the basal secretion tended to diminish. In six patients, acid secretion was studied prior to irradiation by insulin and pentagastrin stimulation (Table I). These patients were matched by age, sex, size and histamine stimulation gastrin analysis, to six patients treated 14 years prior. Shown is the response to insulin and pentagastrin prior to treatment and 14 years later. The response noted then to insulin, pentagastrin and histamine is not unlike that reported by Johnston[6] to the highly selective vagotomy operation.

Of those patients at risk following irradiation, 48 (11.3%) died during the 14-year period of observation; none died from ulcer, ulcer complications or gastric malignancy. Postmortem information was available on 14 patients and death-certificate information, on 34. Of the entire group, 42 patients, or less than 10% of the population at risk, had recurrence of ulcer after treatment. Thirteen of these underwent surgery of whom nine died within one year of their gastric surgery. The mean age of this recurrent group was 50.4 years as compared to the mean age of the entire group, 63.2 years. Recurrent ulcer was documented by either x-ray, endoscopy or surgery.

Clinical response and objective evaluation was uniformly good. The question of renal injury produced by irradiation was addressed by creatinine clearance in 36 patients and urinalysis in all patients and reference to renal injury could not be detected. Schilling tests before and after treatment were unchanged. The effect of irradiation on serum gastrin in six patients did not demonstrate a consistent pattern of change. The cost of the peptic ulcer disease was reduced in spite of the inflationary trend of medical costs. Finally, the record review was impressive in exhibiting many patients who, over the years, were treated with ulcerogenic drugs (aspirin, steroid, phenylbutazone, rauwolfia, etc.) following their irradiation and in whom recurrent ulcer reactivity was not recognized.

## COMMENT

The rationale for gastric irradiation as a method of control of gastric acid secretion lies essentially in its simplicity and its effectiveness. The patient who is a poor risk for surgical therapy often has problems with long-term medical therapy as well. A single intervention of ten or 12 daily irradiation treatments directed at the gastric secretory mucosa is painless, easily tolerated and almost totally without immediate side-effects. The requirement for antacid or anticholinergic medication is almost entirely eliminated in our experience. In those few patients who, over the years, experience some mild discomfort, the amounts of antacid or anticholinergic needed are much smaller than those required prior to the irradiation.

We were rather surprised by the persistence of the early favorable results of our therapy. As shown in the tables, the postirradiation stomach does not respond normally to histamine challenge, a result thought to be desirable and customarily achieved by such operations as antrectomy and vagotomy. As the patient ages, there is apparently also some diminution in basal secretory output as well. The combination of depressed basal secretion and impaired ability to secrete acid after stimulation provides a protective state for these severely ill patients. Thirteen of the patients who were first selected for treatment and ultimately underwent gastric surgery were poor operative risks as comfirmed by the fact that nine of them died postoperatively. We feel that the gastric irradiation provided them with an impressive period of relatively good life-quality before ulcer recurrence brought them to surgery. Perhaps they should have received a second course of gastric irradiation rather than surgical intervention.

The exact place in therapy of the newer $H_2$ antagonist drugs has not yet been established and it may be that their long-term safety and efficacy will be sufficient to obviate the need for gastric irradiation. For the patient who is old, has chronic severe pulmonary or cardiac disease, or needs medications for other problems which are known to accelerate ulceration, gastric irradiation as we have employed it is simple, safe and effective.

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*Communication from Abroad*

# Hepatic Bruits in Malignant Liver Tumors

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There have been few reports concerning hepatic bruits in malignant liver tumors, especially in those other than hepatocellular carcinoma. Lately we noticed hepatic bruits in several cases of malignant liver tumors. The murmurs were confirmed by sound recordings. In cases of hepatocellular carcinoma the murmurs were continuous or continuous with late systolic accentuation. In a case of cholangiocarcinoma of the liver the murmur was continuous with late systolic accentuation and in a case of metastatic liver carcinoma it was systolic. These murmurs were considered to be caused by various mechanisms and some of them are discussed in this paper. Hepatic bruits would be a useful aid in diagnosing hepatic tumors.

Arterial murmurs can be heard over the abdomen in patients with various diseases and sometimes even in normal persons.[1, 2] In 1966 Clain reported that, in some liver diseases such as hepatocellular carcinoma and alcoholic hepatitis, abdominal bruits were also auscultated and that they contributed to the differentiation from the other liver diseases.[3] Since then there have been few reports on abdominal bruits in liver diseases and the character of these murmurs has not been fully analyzed. In addition, there has been only one report on hepatic bruits in metastatic liver tumor[4] and no report of bruits in cholangiocarcinoma of the liver. Lately we have studied hepatic bruits in cases of malignant liver tumors hospitalized in our clinic. The results of the study were described and discussed in this paper.

## MATERIAL AND METHODS

One hundred and sixteen cases of malignant liver tumors were admitted to our

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TABLE I

SUMMARY OF CASES OF HEPATOCELLULAR CARCINOMA

| Case | Age | Sex | Complication | Confirmation of diagnosis | Location of major tumor | Character of the murmur |
|---|---|---|---|---|---|---|
| 1 | 60 | M | | Autopsy | Right lobe | Continuous with late systolic accentuation |
| 2 | 43 | M | | Autopsy | Right lobe | Continuous with late systolic accentuation |
| 3 | 26 | F | | Autopsy | Right lobe | Continuous with late systolic accentuation |
| 4 | 49 | M | Liver cirrhosis | Autopsy | Right lobe | Continuous |
| 5 | 57 | M | | Laparotomy | Right lobe | Continuous |

clinic since 1965. We noticed an arterial murmur over the liver in 13 cases and this was confirmed by sound recordings in seven cases. In cases of hepatocellular carcinoma the murmurs were noticed in nine cases (14.1%) and confirmed in five cases (7.8%). In cases of malignant liver tumors other than hepatocellular carcinoma the murmurs were noticed in five cases (9.6%) and confirmed in two cases (3.8%).

In all seven the murmurs were readily distinguished from a venous hum and were not conducted from other parts of the abdomen or from the heart. Posture, respiration and local pressure produced no significant effect on the murmurs. The bruits were loudest over the liver and, in most cases, greatest over the site of the tumor as shown by autopsy, arteriography or isotopic scanning.

## HEPATOCELLULAR CARCINOMA

In five cases of hepatocellular carcinoma, the murmurs were recorded with a phonocardiographic apparatus and analyzed. Details are summarized in Table I. One patient had underlying cirrhosis. Four cases were male and one was female. Confirmation of diagnosis and sites of tumor was made by autopsy in four cases and by exploratory laparotomy in one case. The tumor was mainly in the right lobe in all five cases. In three patients the murmur was continuous with late systolic accentuation and there was no underlying cirrhosis. In the other two patients the murmur was continuous. Tumors were shown on celiac-axis arteriography in all five cases and in one of them arterioportal shunting was clearly shown.

A 49-year old man was admitted to our clinic with complaints of anorexia and lassitude in 1967. The liver was palpable three finger-breadths below the right costal margin. A continuous murmur was heard over the right lobe of the liver (Fig. 1). Hepatic arteriography showed a massive tumor in the right lobe and the presence of arterioportal shunting (Fig. 2). He died two months after admission. At autopsy a child's head-sized tumor in the right lobe and multiple intrahepatic dissemination were observed. The liver showed portal cirrhosis in addition to the tumor.

## LIVER TUMORS OTHER THAN HEPATOCELLULAR CARCINOMA

In two cases of malignant liver tumors other than hepatocellular carcinoma, arterial murmurs were auscultated over the

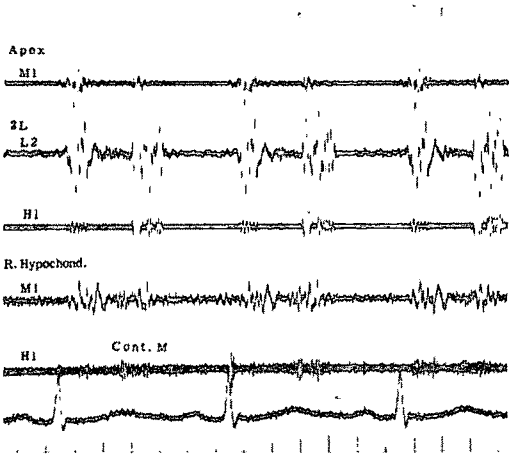

Fig. 1—Phonogram over the right lobe of the liver and precordium (Case 4).

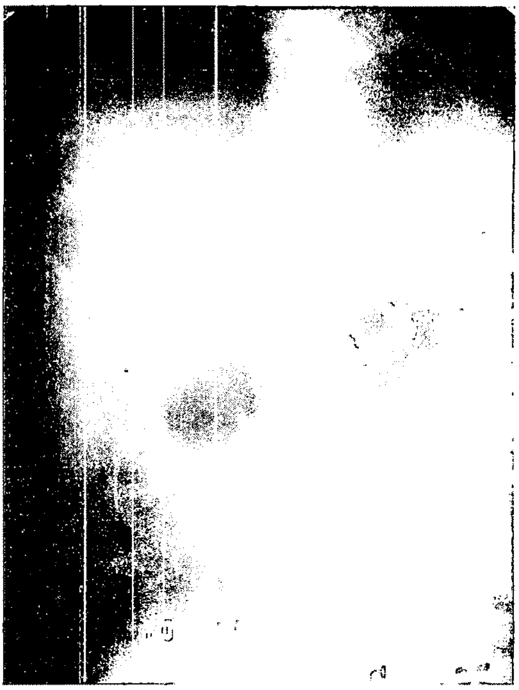

Fig. 2—Hepatic arteriogram showing a massive tumor and arterioportal shunting in the tumor (Case 4).

liver and confirmed by sound recordings. In a case of cholangiocarcinoma of the liver the murmur was continuous with late systolic accentuation and in a case of liver metastasis of adenoid cystic carcinoma of the submaxillary gland the murmur was systolic. These murmurs were considered to be caused by liver tumors as in the cases of hepatocellular carcinoma.

A 38-year old woman was admitted to our clinic in 1968 with complaints of anorexia and icterus. The liver was palpable 3.5 finger-breadths below the right costal margin. A continuous murmur with late systolic accentuation was heard over the epigastric portion of the liver (Fig. 3). Hepatic scanning with $^{198}$Au colloid defined a massive filling defect in the liver. After a month the patient died. At autopsy there was an adenocarcinoma arising in the bile duct at the hepatic hilum, which infiltrated several cm. into the liver, with multiple intrahepatic metastasis of less than walnut size.

A 34-year old woman was operated upon palliatively for adenoid cystic carcinoma of the right submaxillary gland in 1975. After three months she noticed an abdominal tumor and was admitted to our clinic. A hard liver tumor was palpable eight finger-breadths below the right costal margin. A late systolic murmur was heard over the liver in the epigastrium (Fig. 4). Laparoscopy and abdominal aortography confirmed a large liver tumor due to metastasis of the adenoid cystic carcinoma. After a month she was discharged without improvement.

## Comment

When carefully sought for, vascular murmurs have not uncommonly been found in various states and diseases. In normal persons innocent murmurs and a murmur over the inferior vena cava were frequently heard.[1, 2] In a variety of vascular and neoplastic diseases the presence of murmurs has contributed to the diagnosis. Vascular murmurs, audible in the upper abdomen, consist of arterial murmurs and venous

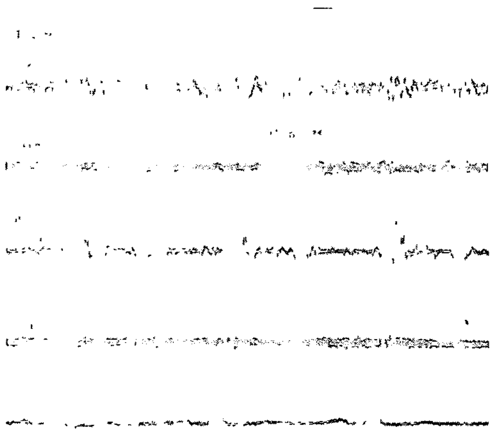

Fig. 3 Phonogram over the epigastric portion of the liver and precordium (case of cholangiocarcinoma of the liver).

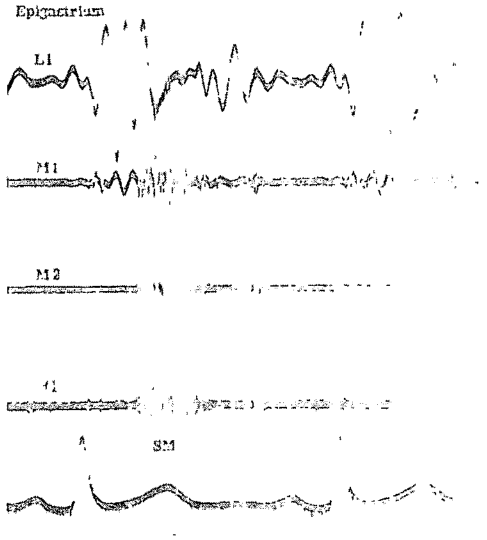

Fig. 4—Phonogram over the epigastric portion of the liver (case of metastatic liver carcinoma).

hum. A representative example of venous hum is that caused by collateral circulations of portal hypertension. The diseases in which arterial murmurs can be heard in the upper abdomen are renal arterial diseases,[5] aortic thrombosis,[6] pancreatic carcinoma,[7] splenic arteriovenous fistula,[8] splenomegaly,[9] tortuous splenic artery,[10] hepatocellular carcinoma,[3] alcoholic hepatitis[3] and fistula between hepatic artery and portal vein.[11]

In 1961 Benner described a case of hepatocellular carcinoma who showed a systolic bruit over the liver tumor.[12] In 1966 Clain reported several cases of hepatocellular carcinoma and alcoholic hepatitis in which liver arterial murmurs were heard. He confirmed these murmurs by sound recordings.[3] Since then, there have been few reports discussing hepatic bruits in malignant liver tumors.

Arterial murmurs in hepatocellular carcinoma are considered to be caused by various mechanisms such as unusually increased blood flow and partial obstruction of a vessel due to infiltration or compression. The vessels in the tumor are wide, thin-walled, and tortuous and are perfused only by the blood from hepatic artery.[13] It is presumed that the murmur is produced as a large volume of blood passes turbulently from a high-pressure arterial system into the low-pressure vessels of the hepatocellular carcinoma.[3]

The occasional presence of some shunts between the hepatic artery and the portal vein in tumors of hepatocellular carcinoma were described.[14] In our clinic such shunts were confirmed in five of 20 cases of this tumor who were examined by hepatic arteriography. Case 4 is an example of this type of shunt. These findings indicate that arterioportal shunts are not infrequent present in cases of hepatocellular carcinoma. As arterial murmurs are commonly heard over the liver in cases of congenital or traumatic arteriovenous fistula of the liver,[11] some of the murmurs of hepatocellular carcinoma may be caused by arterioportal shunts.

The arterial murmurs recorded in our cases of hepatocellular carcinoma were continuous in two cases and continuous with late systolic accentuation in three cases.

Continuous murmur is caused by the passage of blood between the different vessel systems with high pressure gradient and is occasionally accompanied with late systolic accentuation. For example, continuous murmur with systolic accentuation is heard in hepatic arteriovenous fistula, in splenic arteriovenous fistula and in renal artery stenosis with poststenotic dilatation. Continuous murmur of venous origin differs from that of arterial origin as the former is low pitched, is liable to be altered by posture, respiration or local pressure and may be accompanied with diastolic accentuation. On the other hand, systolic murmur was also reported as a pattern of hepatic bruits in hepatocellular carcinoma.[3] As systolic murmur is generally caused by partial obstruction of a vessel, such as renal vascular diseases and compression of splenic artery by pancreatic carcinoma, it may imply compression of vessels by tumor, infiltration of tumor into vessels, or tortuous vessels of tumor, when it is heard over the liver in a case of hepatocellular carcinoma.

There has been no report of hepatic bruits in cholangiocarcinoma of the liver and only one case in metastatic liver carcinoma. In 1967 Warter reported a rough systolic murmur which was heard over the liver tumor in a case of liver metastasis of lung carcinoma, confirmed by sound recordings.[4] In the present paper, we report hepatic bruits heard in a case of cholangiocarcinoma of the liver and a case of metastatic liver carcinoma. The murmur of the cholangiocarcinoma was continuous with late systolic accentuation. At autopsy any notable vascular changes, which could explain the mechanism of the murmur, were not confirmed anatomically. The murmur of the case of metastatic liver carcinoma was late systolic. This murmur was certainly different from the aortic sound because the latter is early systolic in phase and of short duration. These cases demonstrated the presence of audible arterial murmurs over liver tumors other than hepatocellular carcinoma, including metastatic liver carcinoma and such tumors should also be taken into consideration when an arterial murmur is heard in the upper abdomen.

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# Neurohypophyseal Regulation of the Exocrine Pancreas

## A REVIEW

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Antidiuretic hormone can depress normal animal and normal human pancreatic exocrine secretions and modify experimentally induced pancreatitis in animals. No studies have been carried out on man that demonstrate any efficacy of ADH in the treatment of the diseased pancreas.

### INTRODUCTION

Much attention has been given to the myriad of factors that play a part in the cause and pathogenesis of pancreatitis and many developments in this area had to await antecedent studies on the normal function of this gland. Most attention has been given to the effect on pancreatic function of alterations in various physiologic and pharmacologic parameters and relatively little attention has been paid to the role of hormones in the regulation of pancreatic function in normal and disease states. This review is an attempt to summarize the current information available on this subject for the endocrine gland, the neurohypophysis.

### EFFECT OF ADH ON THE EXOCRINE PANCREAS

*Animal pancreatic exocrine flow:*—In the rabbit, antidiuretic hormone (ADH) reduced the pancreatic volume and the bicarbonate concentration and increased the chloride concentration in the intact animal but had no effect in the *in vitro* preparation.[1] In the anesthetized cat with the pylorus ligated and the pancreatic juice stimulated with secretin, posterior pituitary extract abolished the secretory response.[2] The intravenous injection of ADH into anesthetized dogs reduced the pancreatic volume stimulated by endogenous or exogenous secretin.[3, 4] In unanesthetized dogs stimulated by endogenous[4, 6] or exogenous[4, 5, 7, 8] secretin, intravenous injections of ADH also depressed pancreatic exocrine secretion.[4, 8] A direct relationship was noted between the percentage inhibition of pancreatic flow and the dose of the ADH administered, [7-9] with as little as 0.75 m. units of ADH/kg. or 0.012 m. units/ml. causing a decrease in the pancreatic volume.[8] Furthermore, during the ADH inhibition of the pancreatic volume, the sodium,[4-6, 9] the potassium,[7] the bicarbonate[7] and the osmolality[5, 6, 9] of the pancreatic juice remain unchanged, while the protein,[3, 7] the amylase,[5, 7, 9] the lipase[4] and the trypsin[4] concentrations increased. Other investigators, however, reported that after ADH the pancreatic bicarbonate showed a slight decrease[5, 6, 9] and the potassium[4-6, 9] occasionally increased. It was also observed

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that sodium hydroxide, sodium thioglycollate and ultraviolet light, all of which destroy ADH, destroy this pancreas-inhibiting factor.[7] In addition, intravenous injections of hypertonic solutions of sodium chloride or glucose, which increase the release of ADH, also reduce the rate of pancreatic exocrine flow.[7] Finally, it was observed in one study[8] that an alteration in the molecular configuration of ADH modified its ability to inhibit secretin-stimulated pancreatic exocrine secretion. Octapressin seemed to induce a greater and longer inhibition of pancreatic flow than pitressin, which is a mixture of arginine and lysine preparations, while Desamine-cys-1-8-D-arginine had no inhibitory effect.

*Human pancreatic exocrine flow:*—The intravenous injection of ADH into a patient with a pancreatic fistula was found to decrease the basal pancreatic volume, with 0.7 m. units/kg. causing a 37% volume decrease and 1.0 m. unit /kg. resulting in a 56% volume reduction.[10] When the pancreatic secretion in man was assayed by duodenal suction, both posterior pituitary extracts[3] and ADH injections[11] decreased the secretin-stimulated volume.

*Pancreatic blood flow:*—The infusion of 10 m. units ADH/kg./min., into rabbits produced evidence of cardiac ischemia, which was interpreted as also reducing blood flow to the pancreas[1] while the infusion of 10 m. units ADH/kg./min. into dogs reduced blood flow to the pancreas by the $^{42}$K clearance technic.[12, 13] In one study,[7] however, 20 m. units ADH/kg., given intravenously, did not alter the pancreatic venous outflow. More recently[14] labeled microspheres and the bromsulfthalein dye dilution technic were used to measure the hemodynamic affects of ADH in dogs. In the normovolemic animal, the cardiac output fraction of duodenum-pancreas was reduced 46% with 0.75 m. units ADH/kg./min. and 80% with 5.7 m. units ADH/kg./min. while in the hypovolemic animal stabilized at a mean arterial pressure of 60 mm. Hg. for 20 minutes, 5.7 m. units ADH/kg./min. increased duodenum-pancreas blood flow by 20%. In 1976[15] regional blood flow was measured electromagnetically in anesthetized dogs. ADH reduced blood flow in most of the vascular areas. The greatest reduction in blood flow was seen, however, in the gastrointestinal area especially in the left gastric artery, cranial and caudal pancreaticoduodenal arteries, as well as the cranial and caudal mesenteric arteries. In addition, renal blood flow was not altered by those concentrations of ADH that reduced gastrointestinal blood flow. The ADH reduced the pancreaticoduodenal blood flow in concentrations comparable to those concentrations that reduced canine pancreatic secretory flow. Whereas, however, ADH inhibited pancreatic blood flow for two minutes, the pancreatic exocrine flow was inhibited 10-15 minutes.

*Pancreatic disease in animals:*—By the use of two different models to experimentally induce canine pancreatitis, the infusion of a mixture of blood, trypsin and bile into the pancreatic duct under 200 mm. Hg. pressure[16] and the closed duodenal loop technic,[17] pretreatment with ADH modified the course of the disease. The survival rates of these animals were significantly increased,[16, 17] the peritoneal fluid volume and amylase concentrations were reduced[18] and the pancreatic acinar tissue disruption was prevented.[18] When acute hemorrhagic pancreatitis was first allowed to develop by the closed duodenal loop technic, treatment with ADH resulted in a reduction in the ascitic volume and amylase concentration, the fluid was less bloody and no lipid droplets were seen.[19] Since the character of the peritoneal fluid may be a mirror of pancreatic pathology, ADH may have modified pancreatic deterioration and/or increased reabsorption of the ascitic fluid. Pancreatic exocrine secretion was recently measured in dogs that had been subjected to acute hemorrhagic pancreatitis by the closed loop technic and this data was compared to our control pancreatic exocrine secretion data.[20] First, a direct relationship was observed between the percentage inhibition of secretin-stimulated pancreatic exocrine flow and the dose of ADH administered to dogs with acute hemorrhagic pancreatitis. Second, the acute hemorrhagic pancreatitis reduced the sensitivity of the exocrine pancreas to both secretion and to ADH. A three-fold stimulatory dose of secretin was required to produce a comparable pancreatic stimulation in control dogs and a seven-fold inhibitory dose of ADH was required to produce a comparable pancreatic inhibition in control dogs.

Finally, the effects of an intravenous infusion of 4.5 units ADH/kg. over six hours were determined on the aortic blood pressure and the pancreatic blood flow of control dogs and dogs subjected to acute hemorrhagic pancreatitis.[21] In control dogs, ADH increased the blood pressure and decreased pancreatic blood flow by 35-45%. In dogs with acute hemorrhagic pancreatitis, ADH maintained the blood pressure at about control values and increased pancreatic blood flow above control levels.[21]

*Pancreatic ductal pressures:*—No reports could be found in the literature dealing with action of ADH on pancreatic duct pressure.

*Mechanisms of action:*—There is probably enough experimental data to demonstrate that a close correlation exists between the posterior pituitary and the exocrine pancreas. First, a direct relationship was noted between the percentage inhibition of pancreatic flow and the dose of ADH administered with as little as 0.75 m. units ADH/kg. sharply reducing canine pancreatic exocrine flow. Second, an alteration in the configuration of the ADH molecule modified the amount of the pancreatic inhibition. Third, whereas ADH reduced pancreatic blood flow in concentrations comparable to those concentrations that reduced pancreatic exocrine flow, the blood flow was reduced for only two minutes while the exocrine flow could be depressed for 10-15 minutes.

The data also demonstrate that ADH may modify the course of experimentally-induced acute hemorrhagic pancreatitis. First, pretreatment with ADH increased the survival rates, decreased the ascitic fluid and prevented acinar tissue disruption in dogs with acute hemorrhagic pancreatitis. Second, posttreatment of acute pancreatitis in the dog with ADH resulted in a reduction in the peritoneal fluid volume and a change in the characteristics of this fluid. Third, ADH increased pancreatic blood flow in dogs subjected to acute hemorrhagic pancreatitis or to hypovolemia. Finally, the sensitivity of the exocrine pancreas to ADH is modified by pancreatitis.

The mechanism(s) for the above actions of ADH are speculative since little or no cellular biochemical or physiological experiments using ADH have been carried out on pancreatic exocrine tissue. The readers, however, can be referred to two reviews of the literature[22, 23] that deal with a number of theories on the possible action(s) of ADH on cell membranes. These theories include: 1. a pore theory that proposes that ADH accelerates osmotic flow of water by increasing the size (and/or number) of existing aqueous channels in a limiting cell membrane; 2. a series-barrier hypothesis that suggests that the epithelial cell has a minimum of two barriers in series, one an ADH-insensitive diffusion barrier of fixed permeability and the other a vasopressin-sensitive porous structure; 3. a cyclic 3′,5′-AMP generation in the membrane theory that claims that ADH activates adenylate cyclase which in turn generates cyclic AMP which results in an increase in the membrane permeability to water urea, sodium and many other solutes. Therefore, the experimental data presented in the present review, the ADH reduction of pancreatic volume, the ADH decrease in ascitic fluid and the altered sensitivity of the damaged pancreas to ADH, support the theory that ADH acts on the cell membranes to modify the flow of fluids. Perhaps, we should view ADH as modifying fluid movements in all epithelial membranes since it has been shown to act on salivary glands, stomach, pancreas, small bowel and kidneys.

## THE EFFECTS OF OXYTOCIN ON THE EXOCRINE PANCREAS

Intravenous injections of 8-83 m. units oxytoxin/kg. into three dogs failed to alter the rate of pancreatic flow in the unanesthetized dog.[7] In one experiment in which oxytocin was administered simultaneously with ADH in a dose of 83 m. units oxytocin/kg. to 4.1 m. units ADH/kg., there was no augmentation of the inhibitory effect of ADH alone.[7]

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*Communication from Abroad*

# Crohn's Disease of the Appendix, Manifested as Acute Appendicitis with Postoperative Fistula

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Two cases are reported of Crohn's disease localized to the appendix and manifested as acute appendicitis; after appendectomy a fistula developed. In none of 18 patients with Crohn's disease reported by other authors, where the appendix was the primary site, did a fistula develop postoperatively. When the appendix is the primary site of Crohn's disease the presence of mild inflammation of adjacent organs such as the terminal ileum may be mistakenly attributed to ordinary appendicitis. If, at exploratory laparotomy performed on a tentative diagnosis of appendicitis, Crohn's disease is suspected in the adjacent intestine, it is proposed that appendectomy should be followed by at least 10 days of total parenteral nutrition to minimize the risk of a fistula developing.

## INTRODUCTION

A report on Crohn's disease of the appendix manifested as acute appendicitis has recently been published.[1] In none of 18 cases of Crohn's disease where the appendix was the primary site did a fistula develop.[1-12] Most of these patients presented all the clinical signs of acute appendicitis. In several of them, however, not only appendectomy,[1-3, 6, 9-11] but also a resection of the terminal ileum and the right colon was performed.[4, 5, 7, 8, 12] Some authors consider that incidental appendectomy in a patient with Crohn's disease is contraindicated except when the appendix and cecum are not involved, the main concern being that a fistula may develop at the site of the appendectomy. When the disease is obviously present in the terminal ileum or cecum the decision is less straightforward.[13]

The occurrence of Crohn's disease confined to the vermiform appendix is rare, although it has been known since Meyerding and Bertram reported a case in 1953.[2] Crohn, Ginzburg and Oppenheimer[14] held that ileitis does not affect the appendix but it has become evident that the appendix certainly can be involved, usually concurrently with the cecum or the terminal ileum.[15, 16]

The two cases reported here illustrate the risk associated with appendectomy when the vermiform appendix is or seems to be the primary site of Crohn's disease.

## CASE REPORTS

*Case 1:*—A female, 19 years old, one year prior to admission to Huddinge Hospital for appendectomy had suffered from acute cholecystitis, for which five months later cholecystectomy and choledocholithotomy were performed. For two weeks prior to admission there was increasing abdominal pain located in the lower middle part of the abdomen and radiating to the left posterior side. During the week prior to admission she had had watery diarrhea with two or three bowel movements a day but no nausea or vomiting.

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The last two days her temperature was elevated. There was no history of urinary complaints and she had never been pregnant. There were no menstrual abnormalities.

Examination in the Department of Gynecology revealed tenderness to palpation of both the right and left lower abdominal quadrants but no palpable mass. Vaginal examination, however, disclosed a tender ill-defined swelling about 8 cm. across, located to the right of and near the uterus. On admission the rectal temperature was 38.9° C and the ESR, 102 mm./hr.; the urinary sediment was unremarkable. Acute salpingitis was diagnosed and antibiotics (pivampicillin, doxycyclin and cephalexin) were administered for five weeks. After 17 days the swelling could no longer be felt but the ESR was still high at 70 mm./hr. After five weeks the mass had reappeared in the same place and the ESR was 67 mm./hr.

Laparoscopy showed an apparently normal uterus and left adnexa but the right uterine tube was somewhat inflamed, although not enlarged. The appendix was swollen and inflamed. At exploratory laparotomy the entire appendix appeared dark and fibrotic with some edema and it was about the size of the little finger. It was adherent to the terminal ileum, which was slightly inflamed and swollen with edema. The changes in the terminal ileum were ascribed to the appendicitis. Appendectomy was performed.

Microscopic examination of the appendix showed inflammatory alterations and an abscess, surrounded by marked fibrosis and areas of lymphocytic infiltration. There was, however, no convincing histologic evidence of Crohn's disease.

Ten days after the appendectomy there was recurrence of diarrhea and fever, which were temporarily alleviated with ampicillin. During the next two months there were abdominal pain, diarrhea, vomiting, elevated temperature and steady loss of weight. Incision of a subcutaneous abscess in the right lower abdominal quadrant, three months after the appendectomy, disclosed a fecal fistula. The enterocutaneous fistula did not close. At laparotomy four months later, a large inflamed mass was found; it involved the terminal ileum and the cecum and was suggestive of Crohn's disease. There was rupture of the terminal ileum about 5 cm. from its end. The terminal ileum and cecum were removed and microscopic examination showed inflammatory alterations indicative of Crohn's disease.

Four months later a new fistula opened in the abdominal wall and a radiographic examination—performed six months after the ileocecal resection—showed it to originate in the intestinal anastomosis. One month later a perianal fistula appeared.

Fifteen months after the appendectomy oral feeding was stopped and total parenteral nutrition (TPN), including the fat emulsion Intralipid 20%, was introduced and continued for 71 days. During this period the perianal fistula healed and the condition of the skin around the enterocutaneous fistula in the right lower abdominal quadrant improved. After the TPN therapy the remaining fistula with adjacent intestine was excised; recovery was uneventful.[17]

*Case 2:*—A female, 17 years old, one year prior to appendectomy, had acute salpingitis. Four days before the operation she had increasing abdominal pain and on the last day the temperature was 38° C but there was neither vomiting nor diarrhea. Examination on admission revealed tenderness in the lower right abdominal quadrant but no palpable mass. Rectal examination

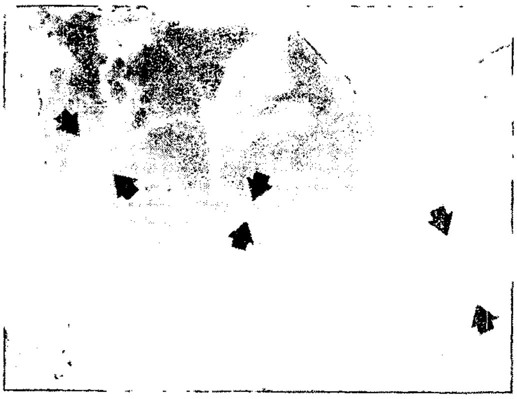

Fig. 1—Case 2. The terminal segment of the ileum (arrows) two months after the appendectomy. There is evidence of Crohn's disease, such as irregular stenosis associated with rigidity and separation of the bowel loops.

disclosed tenderness, especially on the right.

Exploratory laparotomy, performed on a tentative diagnosis of acute appendicitis, disclosed marked inflammation of the appendix and a perforation near its end. The adjacent ileum and the right uterine tube were also inflamed, a condition that was ascribed to the appendicitis. The appendix was removed and microscopic examination showed the presence of inflammatory alterations, including an abscess but no specific evidence of Crohn's disease.

Two months later the patient complained of abdominal discomfort and the ESR was 68 mm./hr. but the leucocyte count was only slightly elevated at 10,900. Radiographs of the small intestine showed features indicative of Crohn's disease in the terminal ileum (Fig. 1).[18]

Ten weeks after the appendectomy a subcutaneous abscess in the right lower abdominal quadrant was drained. This lesion did not heal and proved to be the opening of a persistent enterocutaneous fistula. At this time diarrhea began and increased over a period of time to about three bowel movements a day.

Six months following the appendectomy a second exploratory laparotomy revealed pronounced inflammation of the terminal ileum and the cecum. It is from this area that the fistula originated. There was also adhesion of the sigmoid colon, with an internal fistula. The two fistulas were excised separately with about 50 cm. of the terminal ileum and 30 cm. of the ascending colon. The histologic examination indicated Crohn's disease in the resected specimen. The postoperative recovery was uneventful but the diarrhea continued and even increased a little over the next few years. Moreover, there were skeletal pains, especially in the hip-joints.

Five years after the appendectomy the abdominal pain recurred and a tender ill-defined mass was palpated in the right iliac fossa. There was diarrhea with from three to five movements a day and the patient began to lose weight. Radiographs of the small intestine showed recurrence of changes in the remaining terminal ileum consistent with Crohn's disease. Total parenteral nutrition was introduced, and after 44 days the diarrhea had completely abated—for the first time since the appendectomy—and the mass had disappeared.

## COMMENT

Although the intestinal features of Crohn's disease were described as early as the beginning of the nineteenth century,[19] it was only with the lucid and complete account of this entity given by Crohn, Ginzburg and Oppenheimer in 1932,[14] that it became more widely known.[20] Our knowledge of intestinal granuloma can, however, be traced back to a paper by Combe and Saunders published in 1813[21] and another by Abercrombie in 1828[22] but the disease was probably first reported in

1769 by Morgagni.[23] The wide distribution of Crohn's disease in areas of the alimentary tract other than the actual intestine and in nonalimentary sites[24] renders the eponymous term "Crohn's disease" for regional enteritis particularly appropriate.[20]

The inflammatory reaction occurs first in the submucosa where it is most pronounced[25, 26] but later on it assumes a more focal nature and on the mucosal side nodular structures, reminiscent of tubercles, appear.[19] The presence of giant cells is striking. Hadfield[25] found such cells in 13 out of 20 resected intestinal specimens from patients with Crohn's disease.

Although the appendices of the two patients in the present study displayed no conclusive histologic evidence of Crohn's disease, it was clear from the postoperative course that the appendix was probably the primary site of this disease, and that the inflammation of the adjacent ileum observed at appendectomy was probably an early manifestation of Crohn's disease.

In the case of appendicitis an abscess may mask evidence of Crohn's disease, such as the presence of granulomas and giant cells. In the early stage of the disease, moreover, these may be absent,[26] or so few as to escape detection.[27] The presence, however, of Crohn's disease will probably be revealed by the subsequent clinical course.[19, 28]

The occurrence of nongranulomatous appendicitis in the course of Crohn's disease has been reported[29, 30] but it must be difficult, if not impossible, to distinguish it from Crohn's disease of the appendix—both for the above reasons and because Crohn's disease can involve several discrete sites, leaving the intervening areas unaffected.[18, 27] The presence of granuloma in Crohn's disease has been regarded as a favorable prognostic sign.[31]

It is rare that the appendix is the primary site of Crohn's disease. Out of 18 patients in whom this affection was reported to have been manifested as appendicitis and in whom the pathologic findings were consistent with Crohn's disease only three experienced a recurrence.[6, 9] While it is known that *Yersinia enterocolitica* may produce inflammation of the terminal ileum,[32, 33] the microscopic picture is not familiar.[34] In some of the 15 cases of Crohn's disease manifested as acute appendicitis, where there was no reported recurrence,[1-5, 7-12] the cause may have been *Yersinia* infection; the prognosis for such patients is much better than for patients with the chronic form of Crohn's disease.[35]

It is difficult to make a preoperative diagnosis of Crohn's disease of the appendix solely on the basis of a physical examination and chemical laboratory tests; the regular form of appendicitis often cannot be ruled out. Moreover, appendicitis can simulate Crohn's disease.[36]

In only five of the 20 cases of Crohn's disease where the appendix was the primary site was a preoperative x-ray examination of the colon or the small intestine performed,[8, 11, 12] despite the fact that no abdominal exploration was done until up to five weeks after admission, or until the patient was readmitted after six weeks for appendectomy.[1] In only one of the 20 patients was Crohn's disease suspected before the operation. In that case appendiceal abscess was tentatively diagnosed on the basis of radiographic appearances.[12]

The chance of detecting Crohn's disease in those cases where involvement of the appendix is suspected may be increased if, where the clinical course allows, a preoperative examination of the small intestine is made by means of duodenal intubation with the method of Sellink.[37]

Fecal fistula after appendectomy in Crohn's disease has been reported often to have arisen from the diseased ileum and not from the appendiceal stump.[30, 38] In such cases it has been ascribed to manipulation of the small bowel, rather than to the actual appendectomy.[38, 39] Moreover, in patients with Crohn's disease where an exploration was made on suspicion of appendicitis but where appendectomy was not performed, no fistula developed.[30]

There are several reports of cases where a TPN regimen has resulted in remission of Crohn's disease and healing of the fistulas.[40-44] During prolonged TPN given to one female patient as the primary treatment for advanced Crohn's disease involving the terminal ileum and the whole colon, complete remission of radiologic evidence of inflammation of the appendix was achieved (unpublished observation by Jacobson, et al). This suggests that the appendix might be left in place even if, at laparotomy, inflammatory changes—without imminent or actual perforation—indicate the presence of Crohn's disease of the appendix or the adjacent intestine, if preoperative radiographs have indicated the same disease and if long-term postoperative TPN is intended.

Because appendectomy performed in patients with Crohn's disease manifested as acute appendicitis or ileitis may lead to a fistula,[19, 45-47] the postoperative administration of TPN[48] for at least 10 days is worth trying when the removed appendix or, particularly, the remaining adjacent intestine is suspected of being the site of the Crohn's disease. During this period histologic examination of the appendix may confirm the diagnosis of Crohn's disease, bacteriologic and serologic tests for *Yersinia* infection may prove negative and radiographs of the terminal ileum may rule out or confirm the presence of Crohn's disease. The results of these examinations may serve as a guide to further treatment. The question of whether to undertake appendectomy in Crohn's disease may not arise if prolonged TPN is instituted.

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*Clinical Vignette*

# Umbilicated Gastric Polyposis

## AN INDICATOR OF METASTATIC GASTRIC TUMOR

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A case of multiple centrally umbilicated gastric polyps is presented. Several endoscopic biopsies of the various polyps rapidly established the histological diagnosis of amelantoic melanoma. The significance and differential diagnosis of this endoscopic lesion is discussed.

Gastric polyposis is not infrequently encountered by practicing gastroenterologists. Schindler reported that 1.5-2% of all patients examined by gastroscopy have benign gastric tumors.[1] The incidence of gastric polyps at autopsy varies from 0.2-0.4%.[2] It is not widely recognized, however, that multiple gastric polyps with central umbilication are strongly indicative of metastatic gastric tumor from primary lesions such as melanoma, breast, pancreatic, or bronchogenic carcinoma. The following case illustrates that the awareness of this fact can lead to an early recognition and diagnosis in such a clinical setting.

### CASE REPORT

R. A., a 54-year old white male taxi driver, first presented in October 1975 with chief complaint of soreness of the left wrist and a 9 kg. weight loss. Physical examination revealed a slightly swollen and tender left wrist and a palpable mobile supraclavicular lymph node. Barium meal x-ray study revealed multiple polypoid lesions in the gastric antrum and the duodenum (Fig. 1). Endoscopy showed multiple, umbilicated, sessile, nonpigmented polyps in the antrum and duodenal bulb (Figs. 2 and 3). Several biopsies from different

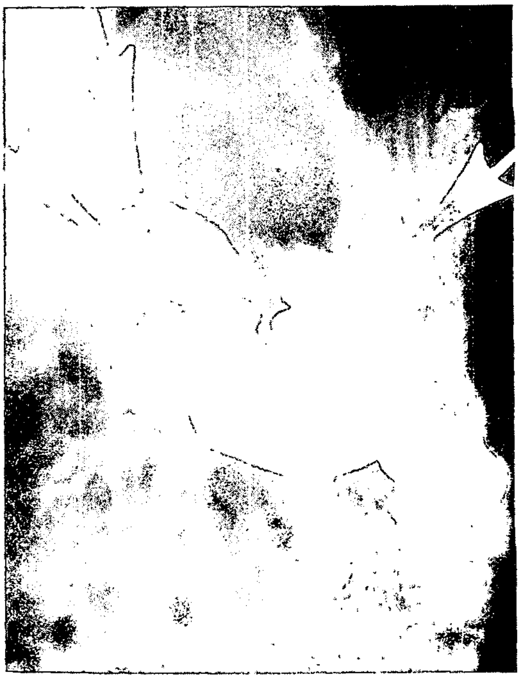

Fig. 1—Upper gastrointestinal series showing filling defects in the stomach and duodenum.

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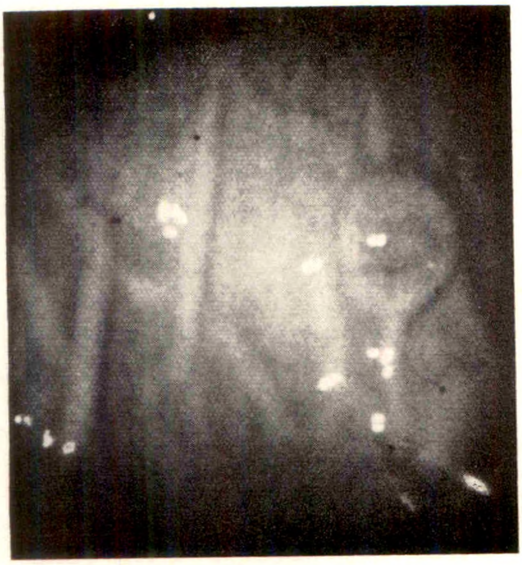

Fig. 2—Solitary sessile umbilicated gastric polyp as seen on gastroscopy.

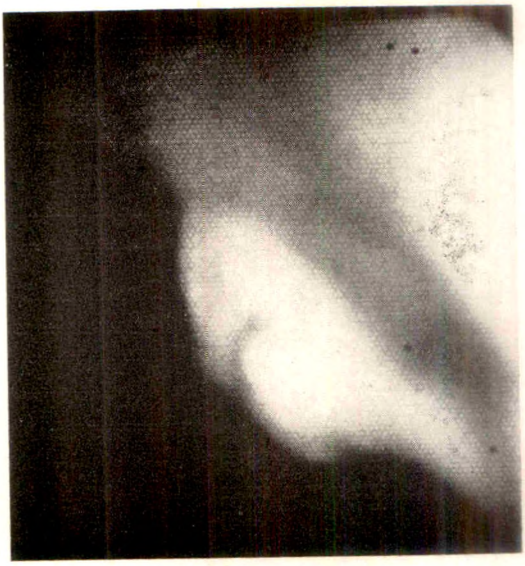

Fig. 3—Side view of the umbilicated gastric polyp as seen on gastroscopy.

polyps were obtained. These revealed poorly differentiated adenocarcinoma. Similar changes were seen on cervical lymph node and left distal radius biopsies. Subsequently, all biopsies were found to be positive for dopamine stain suggesting metastatic amelanotic melanoma.

## COMMENT

Although the stomach is a rather unusual site for tumor metastasis, a large variety of tumors are known to metastasize to this organ.[3] Most commonly, the primary tumors originate in the lungs, breasts, pancreas and colon. Carcinoma of the breast develops gastric metastasis in approximately 8% of all cases.[4] Furthermore, melanoma metastasize to the stomach in as many as 20% of cases.[5] These lesions are usually small, multiple, polypoid lesions, frequently with a central umbilication or ulcerations.[5-8] Sufficient emphasis has not been given, however, to the fact that umbilication or central ulceration of gastric polyps is not confined to metastatic melanoma alone. Other metastatic lesions to the stomach, such as those originating in the bronchus, breast, and pancreas, often give rise to umbilicated polyps.[9]

Curiously, the tendency towards central ulceration is notably seen in metastatic lesions to the stomach and not in metastic tumors to the other parts of the digestive tract.[2, 3, 9] Further, solitary umbilicated polyps may also be seen in tumors, such as lymphoma, gastric carcinoid and Kaposi's sarcoma. Eosinophilic granuloma and frequently heterotopic pancreas, may present as solitary umbilicated sessile polyps. The heterotopic pancreas, however, is almost always located along the greater curvature.

Thus, the presence of multiple sessile polyps with a central ulceration seen on gastroscopy should alert the endoscopist to the strong possibility of metastatic gastric tumor.

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## *Clinical Vignette*

# Plasmacytoma of the Stomach

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A case of gastric plasmacytoma is presented. A detailed study including a selective angiogram described this unusual gastric neoplasm. Pathological examination by both light and electron microscopy confirmed the diagnosis of primary gastric plasmacytoma. The diagnosis and treatment of primary gastric plasmacytoma is discussed and pertinent literature is reviewed.

Extramedullary plasmacytomas occurring in the stomach are exceedingly rare tumors. The vast majority of extramedullary plasmacytomas occur in the upper respiratory tract and conjunctiva. Reports[1-3] have appeared of this tumor being found in the ileum, jejunum and stomach. In 1971, Remigio and Klaum[4] reported a case of extramedullary plasmacytoma of the stomach and reviewed 12 previously reported cases from the literature. In 1953, Stout[5] reviewed four cases of gastric plasmacytoma and reported one case with involvement of the mediastinal node. In 1973, Godard, Fox and Levinson; reviewed the world literature and found 46 cases of gastric plasmacytoma; there were 29 males and 17 females whose ages ranged from 28-86 years. The vast majority presented with epigastric pain.

The present report is that of an additional case of gastric plasmacytoma with an abdominal mass treated by radical gastric resection. Both the light and electron microscopic features are presented as well as the angiographic study of the tumor, an examination not previously described.

## CASE REPORT

A 74-year old black male was admitted to the hospital with discomfort in the left side of the abdomen of 2-3 weeks' duration. Past history revealed a gunshot wound in the left chest many years back. Two years ago an enlarged left cervical node was treated by radiation therapy.

On examination he was found to be fairly-built and slightly anemic. No nodes were palpable in the neck, axilla or groin. The abdomen revealed a large mass in the left upper quadrant extending under the left costal cartilage. The liver was not enlarged. Rectal examination was normal.

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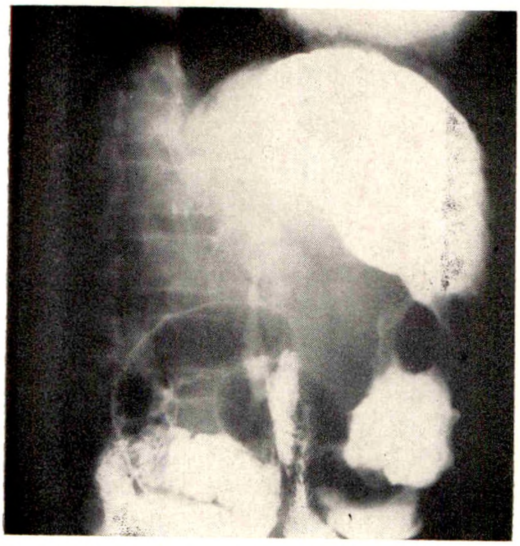

Fig. 1—Barium meal shows a large filling defect with ulcer greater in the posterior wall of the stomach.

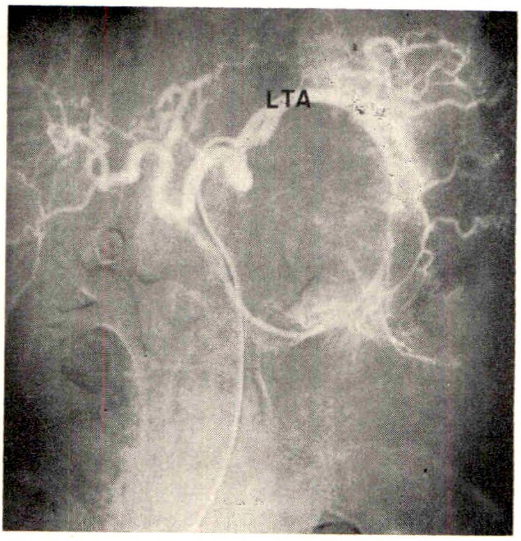

Fig. 2—Selective gastric angiogram showing distortion and displacement of left gastric artery with minimal infiltration by the tumor (LTA).

*Laboratory examination:*—Routine blood, urine and liver chemistries were within normal limits except for an hematocrit of 24%. Chest x-ray revealed a bullet in the left chest and some old scarring. Upper gastrointestinal series showed a large mass involving the stomach (Fig. 1). Lower gastrointestinal series and I.V.P. were normal. Liver and spleen were normal. Bone marrow aspiration and serum electrophoresis were normal. Angiogram of the celiac and left gastric artery revealed a large mass involving the stomach (Fig. 2). Liver, spleen and total body bone scan using gallium showed good uptake; no osseous lesion was noted. Gastroscopy disclosed a large fungating tumor. Biopsy of the mass was reported as showing necrosis and a poorly differentiated malignant tumor.

After preparing the patient and correcting the anemia, he was explored. A large tumor was found involving almost the whole stomach and infiltrating the pancreas and the transverse mesocolon. The mass was resected with Roux-en-Y anastomosis. The patient tolerated the procedure well and went home three weeks after surgery. Examination of the specimen by light microscopy and electron microscopy disclosed plasmacytoma of the stomach. The patient received postoperative radiation therapy and is doing well.

***Pathology:***—Gastrointestinal plasmacytomas are histologically distinctive neoplasms. They differ from conjunctival and upper respiratory tract plasmacytomas which appeared to be inflammatory in nature and show granulomatous features on histology.

Respiratory tract plasmacytomas often occur as a secondary feature of multiple myeloma, whereas gastric plasmacytomas are often present as primary plasmacytomas. Although both of these lesions may present as the first manifestation of multiple myeloma, microscopically one can feel confident that these are true neoplasms with plasma cells collected into extensive solid masses instead of being loosely diffused throughout a vascular granulomatous framework (Fig. 3).

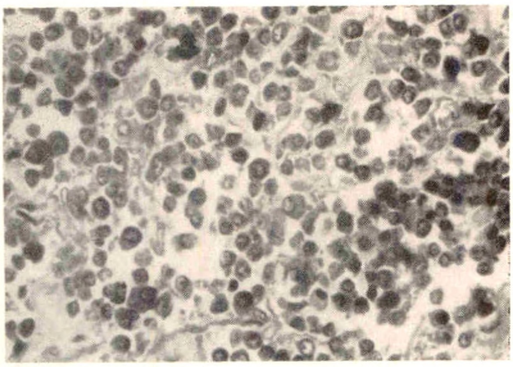

Fig. 3—Microscopic feature of gastric plasmacytoma. Dark eccentric nuclei, often paranuclear zone is seen, some of them have two nuclei (Hematoxylin and eosin, original magnification x300).

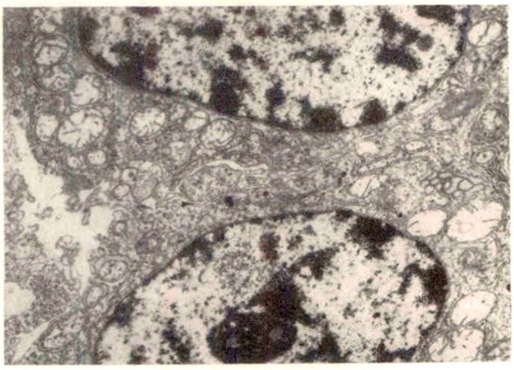

Fig. 4—Electron microscopic features of plasmacytoma. Two plasma cells with cytoplasmic bridge (arrow). They contain moderate amount of peripheral chromatin condensation (original magnification x30,720).

*Electron Microscopy:*—Glutaraldehyde fixed tissues were examined under the electron microscope. Ultrastructurally, the plasma cells had a nucleus with smooth, rounded outline, frequently eccentric, with variable peripheral chromatin condensation according to the maturity of the cells (Figs 4 and 5). This arrangement accounts for the classical clock-face appearance under light microscopy; in less mature cells the chromatin was slight or absent, as observed by Cawley and Hayhoe.[6]

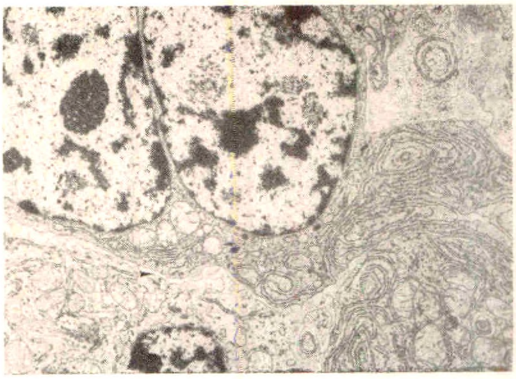

Fig. 5—An immature binucleated plasma cell with moderate chromatin and mitochondria, cytoplasmic bridge (arrow) (original magnification x10,970).

*Angiography:*—A large dilated and upward displaced left gastric and a relatively large right gastric artery supplied several tortuous and dilated vessels invading a neoplasm of the midportion of the body of the stomach (Fig. 2). There was minimal increased contrast accumulation and no evidence of early nenous drainage indicative of lymphomatous disease of the stomach.

Angiography performances in alimentary tract lymphomatous diseases are infrequent. In general, these lesions are poorly vascularized. The angiographic findings are displacement and distortion of vascular anatomy with minimal infiltration by the tumor. There is minimal accumulation of the contrast and no evidence of early venous drainage in capillary phase.

## COMMENT

Couret[7] reported the first primary gastric plasmacytoma in 1945. Merritt[3] reviewed the literature and tabulated 17 such cases in 1955 and subsequently Godard, Fox and Levinson,[1] in 1973, collected 46 cases of gastric plasmacytoma from the world literature. Extramedullary plasmacytomas other than in the stomach and gastrointestinal tract have been reported much more often. They have different histological characteristics and are mostly benign in behavior.

The patient here presented had a node in the neck which was initially thought to be lymphoma. On retrospective review, this proved to be involved by plasmacytoma, perhaps similar to the situation noted by Stout[5] in the mediastinum.

The treatment of gastric plasmacytoma is still a matter of controversy. Most of the previously reported cases were treated by surgery with radiation or chemotherapy but follow-up is limited.

Although these patients may not show any evidence of systemic involvement at an early stage, gastric plasmacytoma may be the prodrome for multiple myeloma and the patient should be followed carefully.

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***Clinical Vignette***

# Traumatic Hemobilia

## DIAGNOSIS BY ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY

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A patient with traumatic hemobilia documented by retrograde endoscopic cholangiography and treated by right hepatic artery ligation, is described. The role of ERCP in making the diagnosis of traumatic hemobilia is discussed.

### INTRODUCTION

Traumatic hemobilia as described by Sandblom in 1948,[1, 2] refers to hemorrhage into the biliary tract following trauma to the liver. The interval between injury and the onset of symptoms is usually prolonged, often up to several weeks. A clinical triad of symptoms includes intermittent, often colicky, right upper quadrant abdominal pain, fluctuating intensity of jaundice and acute upper gastrointestinal hemorrhage. The traumatically induced abnormal communications between the biliary system and its arterial supply may frequently be demonstrated by cholangiography and arteriography.

### CASE REPORT

A 23-year old male was brought to the emergency ward immediately after a fall in which he sustained facial and abdominal trauma. He complained of diffuse abdominal pain and on physical examination there was marked tenderness to palpation over the entire abdomen. A diagnostic abdominal paracentesis yielded hemorrhagic fluid and at exploratory laparotomy a massive intraperitoneal hematoma and right perinephric hematoma were evacuated. The liver was inspected and no evidence of hepatic trauma was noted. During the post-operative week the patient complained of right upper quadrant abdominal and right shoulder pain. Chemistries demonstrated fluctuations in the serum bilirubin (1.1-5.7 mg.%); SGOT (274-380 I.U.) and alkaline phosphatase (85-500 I.U.). Following the recurrence of hematemesis and melena, emergency gastroscopy revealed no bleeding source in the esophagus, stomach or duodenal bulb. The descending duodenum was not visualized. An abdominal ultrasonogram revealed a slightly dilated gallbladder with considerable internal echogenic material (Fig. 1). The biliary system and gallbladder were not visualized after oral and intravenous cholecystography. An attempt at skinny-needle percutaneous transhepatic cholangiography was unsuccessful. Because hemobilia was clinically suspected an attempt was made to visualize the intrahepatic biliary radicles and gallbladder by retrograde cholangiography. During ERCP, active bleeding was seen issuing from the papilla of Vater. After cannulation a dilated common bile duct and cystic duct were demonstrated with multiple filling defects throughout the ducts and gallbladder. The right intrahepatic biliary

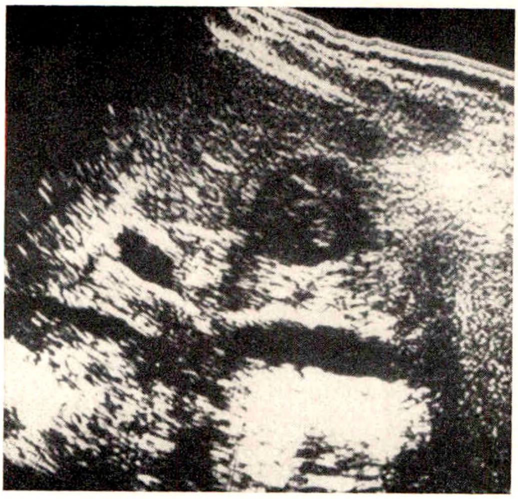

Fig. 1—Abdominal ultrasonogram demonstrating a slightly dilated gallbladder with considerable internal echogenic material.

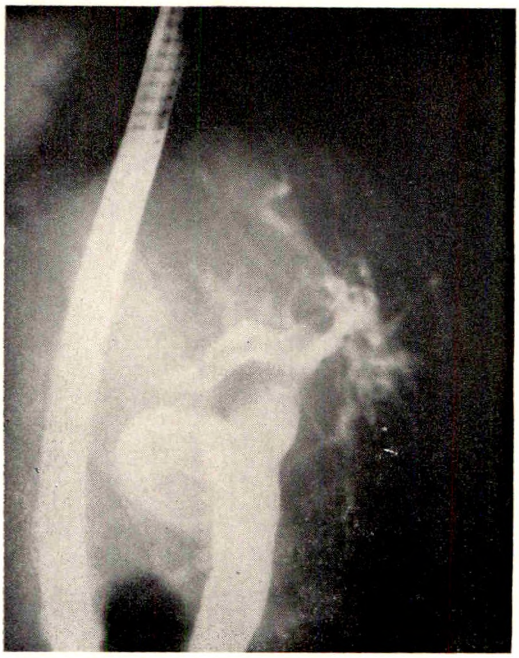

Fig. 2—ERCP: multiple filling defects are seen within dilated common bile duct and cystic duct.

system was poorly visualized (Fig. 2). Immediately following the ERCP an abdominal arteriogram demonstrated an anomolous right hepatic artery arising from the superior mesenteric artery and a false aneurysm within the liver at a terminal segment of the right hepatic artery (Fig. 3). The patient underwent a second laparotomy at which time a dilated common bile duct and gallbladder were noted to contain clots of blood. A cholecystectomy and ligation of the right hepatic artery were performed. At pathological examination the gallbladder was filled with clot adherent to the mucosal wall. Postoperatively, liver tests, including serum bilirubin, SGOT and alkaline phosphatase approached normal values and the patient was discharged.

## COMMENT

Ultrasonography has been described as a useful, noninvasive technic when the diagnosis of hemobilia is suspected.[3] It may demonstrate localized collections of fluid compatible with blood leakage that appear as reduced or echo-free areas within the hepatobiliary system. The confirmation of the diagnosis of traumatic hemobilia requires, however, cholangiographic visualization of the biliary tree and its arterial supply.

Oral cholecystography may demonstrate radiolucent filling defects in the gallbladder and bile ducts compatible with blood clot especially when repeated studies demonstrate alterations in the size and shape of the lucencies. Repeated studies are time consuming and often unrevealing, however, due to poor concentration of dye in a blood filled gallbladder.

Intravenous cholecystography may demonstrate obstructing clots in the biliary tree but this procedure is often rendered unsatisfactory because of fluctuating hyperbilirubinemia secondary to intermittent biliary duct obstruction by clot.

Percutaneous transhepatic cholangiography with the skinny-needle may be helpful in visualizing the biliary system

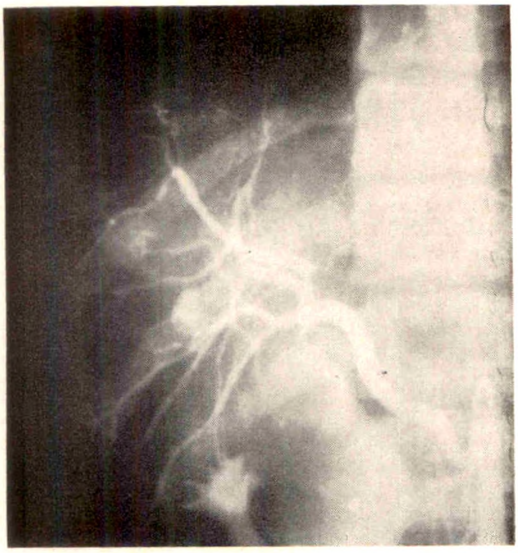

Fig. 3—Abdominal arteriogram demonstrates an anomalous right hepatic artery arising from the superior mesenteric artery; a false aneurysm within the liver at a terminal segment of the right hepatic artery is seen.

even in the absence of dilated intrahepatic biliary radicles. In the patient described, however, the procedure failed to fill any portion of the biliary tree.

ERCP is a rapid and safe technic for the demonstration of abnormalities in the biliary tree and should be considered before other more invasive and time-consuming procedures. Once active hemorrhage from the papilla of Vater is visualized endoscopically,[4] retrograde cannulation and visualization of the biliary tree and gallbladder can be achieved regardless of the level of the serum bilirubin. In conjunction with arteriography the bleeding site(s) can be anatomically and definitively localized. Arteriography is crucial not only to demonstrate the site of abnormal communication between the biliary system and its blood supply but also to demonstrate the distribution of the hepatic artery prior to surgery.

In summary, ERCP and arteriography are complementary studies and when performed in sequence can facilitate the diagnosis of traumatic hemobilia and expidite definitive therapy of a life-threatening condition.

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***Clinical Vignette***

# Rieger's Syndrome Associated with a Large Meckel's Diverticulum

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## INTRODUCTION

A syndrome of hypodontia or partial adontia with malformation of the anterior chamber of the eye was described in 1935 by Rieger;[1] later, he reported that the entity was inherited by autosomal dominance.[2]

It has been suggested that the malformation develops during the fifth or sixth week of intrauterine life. Hypodontia is associated with underdevelopment of the maxilla; the ocular lesions comprise microcornea, corneal opacity, hypoplasia and flattening of the anterior surface of the iris and anterior synechiae.

We have recently treated a patient with known Rieger's syndrome who presented with a large symptomatic Meckel's diverticulum.

## CASE REPORT

A 23-year old Hispanic man was admitted to the hospital because of abdominal pain.

In the six months prior to entry, he experienced periodic crampy abdominal pain, localized principally in the right upper abdomen and epigastrium. The pain lasted at times five to six hours and was occasionally associated with nausea. Two weeks prior to admission, he developed intermittent diarrhea. He was born prematurely to normal parents and weighed 1,650 gm. The ocular anomalies were noted at birth, whereas the dental malformations were observed later. During adolescence, he suffered from blurred vision and an increase in intraocular pressure was found and treated chronically with acetazolamide, (Diamox, Lederle) with a dose of 500 mg./day. There was no evidence for familial involvement by this syndrome.

Physical examination revealed arterial pressure of 120/80, regular pulse at 80/min. and a normal respiratory rate. There was mild obesity (weight 89 kg.) and a height of 167 cm. The corneas were small (microcornea) and measured 8 mm. in diameter (Fig. 1). There were polycoria and prominent keratoconus (Fig. 2). His teeth were infantile and widely separated (Fig. 3).

Detailed ophthalmologic examination showed normal ocular motility without strabismus and the fundi were normal. Uncorrected vision showed marked myopia with the following visual data: *Distance:* Right, 20/8; Left, 20/100; both, 20/80. *Near:* Right, J/2 at 25 cm.; Left, J2/ at 25 cm. and Both J/2, at 25 cm. Refractive measurements were consistent with moderate compound myopic astigmatism in both eyes. Visual field examination showed 35° binasal field constriction. There was a

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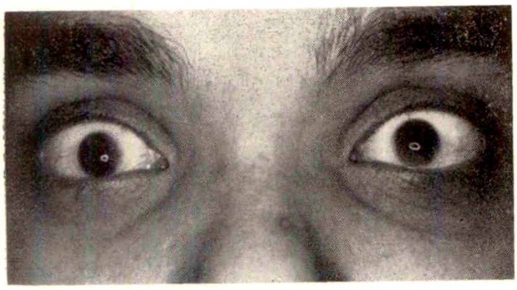

Fig. 1—Microcornea 8mm. indiameter

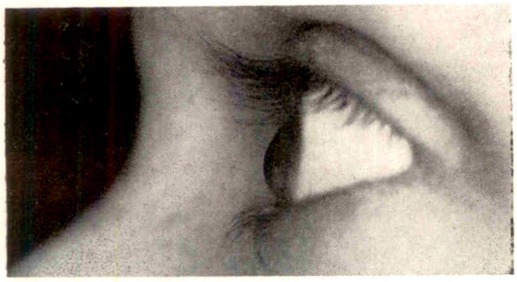

Fig. 2—Polycoria and prominent keratoconus are present.

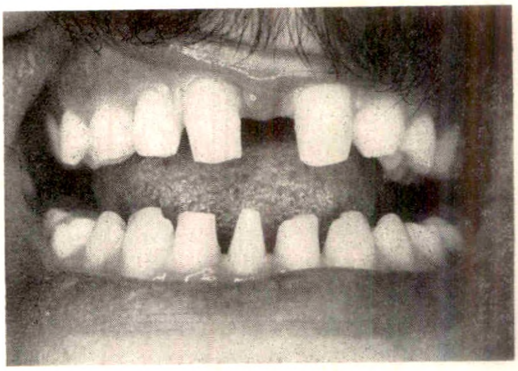

Fig. 3—Teeth are infantile and widely separated.

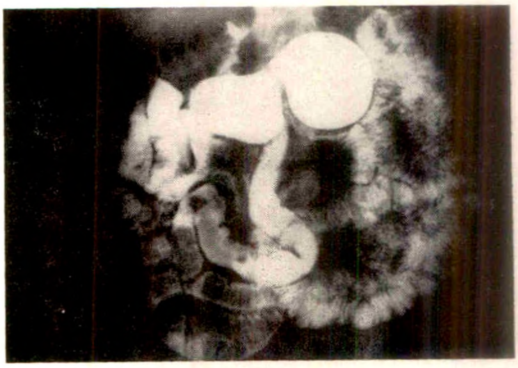

Fig. 4—Large Meckel's diverticulum.

moderate red-green color deficiency and the intraocular pressures based on Schiotz tonometry were: OD, 21; OS, 17.

Examination of the neck, lungs and heart was unremarkable. The abdomen was normal except for mild tenderness in the right upper abdomen. The genitalia and extremities were normal. The skin elasticity and joint movements were normal.

Radiographic contrast studies of the small intestine with late films of the small bowel and colon showed a large Meckel's diverticulum (Fig. 4).

Isotope scanning using $^{99}$Tc pertechnetate showed no increased uptake by the diverticulum.

The remaining laboratory investigations including chest x-ray and ECG were normal.

At laparotomy, a large Meckel's diverticulum was found measuring 12 cm. in diameter and located at a distance of 16 cm. from the ileocecal junction The ileum proximal to the diverticulum was dilated because of partial torsion (volvulus) produced by the diverticulum.

A segmental resection of the diverticulum-bearing ileum and end-to-end anastomosis were carried out and combined with appendectomy. Postoperative convalescence was characterized by transient ileus and microscopic hematuria associated with right flank pain on the eighth postoperative day. Intravenous pyelography during and after the renal crisis showed no definite evidence for a stone; serum uric acid and calcium levels remained normal. He was discharged two and a half weeks after surgery.

## COMMENT

Vossius in 1883 first described this malformation as hypodontia combined with anomalies in the anterior chamber of the eye. The full syndrome was recognized and described, however, by Rieger in 1935 as *dysgenesis mesodermalis cornea et Iridis.*[1, 2]

He also indicated that the syndrome had an autosomal dominant pattern. Ocular findings include: hypoplasia and flattening of the anterior surface of the iris, anterior synechiae, microcornea, glaucoma, ectopic pupils, anterior polar cataracts, optic atrophy, strabismus, deep anterior chamber and pseudohypertelorism.

Busch in 1960 described five generations of a family with this syndrome associated with myotonic dystrophy.[3]

The face is widened resulting in relative prognathism. The premaxillary area is underdeveloped with marked hypodontia. In patients less severely involved, the teeth most commonly missing are the maxillary incisors. Enamel hypoplasia is also present.[4]

A less well known component of this syndrome is anal stenosis described by Crawford in 1967.[5] Schachenmann,[6] in 1965, described a family in which the combination of coloboma of the iris, anal stenosis and renal malformation was inherited in a dominant manner and associated with a specific chromosome aberration, "cat eye syndrome". Alkemade,[7] in 1969, confirmed the autosomal dominant inheritance. He pointed out the characteristic facies consisting of broad nasal root with telecanthus and maxillary hypoplasia with protruding lower lip. A mother and two of three children had severe developmental anomalies of the iris associated with maldevelopment of the ear and maxilla, umbilical hernia and anal stenosis. Glaucoma occurred in all three patients. Growth hormone levels were decreased in most of these patients.[8] Our patient had the characteristic features of Rieger's syndrome with a large Meckel's diverticulum. Patients with umbilical hernia and imperforated anus were described before but asscociation with gastrointestinal anomalies were not described previously.

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*Clinical Vignette*

# Hemoperitoneum from a Ruptured Varix in Cirrhosis

## CASE REPORT AND LITERATURE REVIEW

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A cirrhotic patient with hemoperitoneum is presented. The diagnosis of ruptured retroperitoneal varices was made at laparotomy and the patient becomes the second reported case to survive hospitalization for bleeding intra-abdominal varices. The formation of varices as a consequence of portal hypertension is discussed; the differential diagnosis and evaluation of hemoperitoneum is considered and the seven previously reported cases of intra-abdominal variceal hemorrhage are reviewed.

Esophagogastric varices are, in terms of hospitalization and mortality, the most significant complication of portal hypertension.[1] By far the most frequent cause of portal hypertension in the United States is cirrhosis due to alcoholism[2] and variceal hemorrhage from the upper gastrointestinal tract commonly occurs in these patients.[3] Variceal bleeding into the small intestine,[4-6] colon[6-9] and vagina[10] are also recognized. In some instances, varices arise in postoperative adhesions between the bowel and the parietal peritoneum.[11-13] Massive variceal hemorrhage from colostomy and ileostomy stomas has been described.[14] Less well-appreciated is rupture of intra-abdominal varices into the peritoneal cavity.

## CASE REPORT

A 49-year old white male cirrhotic, a former alcoholic, was admitted to the hospital, having had three syncopal episodes during the preceding two days. There had been neither seizure activity nor residual neurologic deficit. For one week prior to admission, the patient had experienced intermittent crampy lower abdominal pain, unrelated to meals, position or activity. Two days prior to admission, nonbloody diarrhea had developed. There had been no fever or chills and the patient denied any history of abdominal trauma. There was no previous history of convulsive disorder or other primary neurologic dysfunction. The patient had been hospitalized two years earlier for upper gastrointestinal hemorrhage, ascites and hepatic encephalopathy. Nonbleeding esophageal varices were seen endoscopically. Upper gastrointestinal series was normal

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at that time. Since then he has been maintained on spironolactone and antacids.

On physical examination, recumbent blood pressure was 98/50 and pulse was 100. Orthostatic changes were noted so that upon sitting, blood pressure fell to 86/45 and pulse increased to 120. Rectal temperature was 37° C. There was scleral icterus, bilateral gynecomastia and multiple spider angiomata. Cardiac and pulmonary examinations were within normal limits. The abdomen was distended with a fluid wave and shifting dullness. Dilated venous collaterals were present on the anterior abdominal wall and blood flow was caudad in infraumbilical vessels. Bowel sounds were hypoactive but of normal quality. The abdomen was soft, with moderate direct epigastric tenderness. There were no peritoneal signs. The liver edge was not palpable or ballotable. The spleen tip was felt 2 cm. below the left costal margin on inspiration. There was no peripheral edema. Neurologic examination was within normal limits except for asterixis. The remainder of the physical examination was unremarkable.

Electrocardiogram showed sinus tachycardia but was otherwise normal. Chest x-ray was normal. Abdominal flat plate confirmed the presence of free fluid but was otherwise unremarkable. Laboratory data revealed a white blood cell count of 11,600/cu. mm. with a normal differential. Hemoglobin was 7.0 gm. and hematocrit 20 vol.%. Serum chemistries: total protein, 5.5 gm.; albumin, 3.3 gm.; total bilirubin, 4.8 mg.%; alkaline phosphatase, 72 I.U. (normal 15-85); LDH, 330 I.U.; SGOT, 183 I.U., amylase, 48 S-C units (normal 8-33). Prothrombin time was 17.5 seconds (control 12.5). Platelet count was 140,000/cu. mm.

A nasogastric tube returned "coffee-ground" material which intermittently recurred during the initial several days of hospitalization. Paracentesis on the second hospital day revealed bloody, nonclotting fluid with a hematocrit of 26%. Simultaneous peripheral venous hematocrit was 19. Visceral arteriography, including celiac, hepatic, superior mesenteric and aortic injections, revealed moderate splenic enlargement and tortuosity of the intrahepatic branches of the hepatic artery. Neither varices nor a bleeding site was noted. Upper gastrointestinal series was normal. Over the next five days, abdominal girth increased and repeat paracentesis revealed the hematocrit of the sanguinous abdominal fluid had risen to 30%. Vitamin K therapy failed to improve clotting function.

On the ninth hospital day, after having received 17 units of blood and 17 units of fresh frozen plasma, the patient was taken to the operating room. Ten liters of bloody fluid were removed from the abdominal cavity. The liver was noted to be finely nodular and shrunken. A perforated retroperitoneal varix was found to be bleeding into the subhepatic space. Ligation of this vessel resulted in the cessation of bleeding. Postoperative course was uncomplicated and 12 months following discharge, the patient feels well, has no ascites and is working full-time.

## COMMENT

Variceal bleeding is an uncommon cause of hemoperitoneum. In a review of 129 cases, Ellis, et al describe only a single patient with intra-abdominal varices— a 74-year old man presenting in shock with abdominal pain and distention, who at autopsy had massive hemoperitoneum, cirrhosis, esophageal varices and a large retroperitoneal hematoma overlying the right kidney which had ruptured through the parietal peritoneum.[15] Of the six reported cases which were diagnosed antemortem, all were cirrhotics and presented similarly

TABLE I

SUMMARY OF REPORTED CASES OF INTRA-ABDOMINAL VARICEAL BLEEDING IN CIRRHOTICS

| Age | Sex | Presentation | Bleeding site | Outcome | Reference |
|---|---|---|---|---|---|
| 74 | M | Abdominal pain and distention; hypotension | Anterior to right kidney | Died | Ellis, et al[15] |
| 43 | M | Abdominal pain and distention; hypotension | Root of small bowel mesentery | Died | Rothschild, et al[16] |
| —* | M | Abdominal distention; hypotension | Right colic gutter | Died | Miller and Dineen,[17] |
| 38 | M | Abdominal pain and distention; hypotension | Paraumbilical | Survived | Ross[18] |
| 32 | M | Abdominal pain and distention; hypotention | Postappendectomy adhesions | Died | Mall and Grundies[19] |
| 28 | M | Abdominal pain and distention; hypotension | Anterior to right kidney | Died | Doromal, et al[20] |
| 39 | M | Abdominal pain and distention; hypotension | Right colic gutter | Died | Shapero, et al[21] |
| 49 | M | Abdominal pain and distention; hypotension | Anterior to right kidney | Survived | Present case |

* Age not stated

with rapidly increasing abdominal distention and shock. All but one are noted to have had abdominal pain. Rothschild, et al describe a 43-year old man who bled from a ruptured varix at the root of the small bowel mesentery. Their patient died on the second postoperative day with a generalized bleeding diathesis, severe hepatic encephalopathy and acute renal failure.[16] Miller and Dineen describe a fatal case of hemorrhage from varices lateral to the cecum.[17] Ross has reported a male patient who survived laparotomy for plication of a ruptured paraumbilical varix.[18] Intraperitoneal bleeding from varices in a postoperative adhesion has been reported by Mall and Grundies[19] and Doromal, et al have described a cirrhotic with an intrahepatic arteriovenous fistula who survived laparotomy for control of a ruptured posterior peritoneal varix, only to succumb to complications of a massive esophagogastric variceal hemorrhage in the postoperative period.[20] Most recently, Shapero, et al have reported a case of hemorrhage from variceal veins in the peritoneum lateral to the ascending colon.[21] The eight reported cases of hemoperitoneum from intra-abdominal rupture of varices are summarized in Table I.

Resistance to blood flow reaching the cirrhotic liver and the resultant increase in intravenous pressures, may cause dilatation anywhere along the entire portal venous system. The development of anastomoses between the portal and systemic circulations occurs at sites where veins, draining into the two systems, are juxtaposed. This is seen not only in the submucosal esophageal and rectal venous plexuses but also between the umbilical vein remnant and the epigastric veins of the anterior abdominal wall and in the posterior abdominal wall beneath the parietal peritoneum (veins of Retzius).[22] Connections sometimes also form between the capsule of the liver and the diaphragm (veins of Sappey) and between the splenic vein and the left renal vein.[23] Although shunting of blood through portasystemic collaterals may partially decompress the portal circulation,[24] in most cirrhotics portal hypertension persists.

Just as varices are more likely to develop in specific locations, so also may contiguous tissues predispose established varices in different sites to bleed with considerably different frequencies. Esophageal varices do not ordinarily rupture through the *muscularis* into the adventitia of the posterior mediastinum but rather into the esophageal lumen, which probably represents the path of lesser resistance. It is not known how often esophageal varices bleed "spontaneously" and how often variceal hemorrhage is secondary to mucosal injury. The likelihood of bleeding does not correlate with portal venous pressure[25] and the role of esophagitis in the development of varix rupture is insignificant.[26, 27] In the rectum, intraluminal rupture is probably favored by intramural muscle layers and supporting perirectal tissues. Variceal bleeding from the small intestine and proximal colon are rare but it would seem that transmucosal rupture is more common than transserosal. Paraumbilical varices may rupture either cutaneously or into the peritoneum but do so uncommonly in the absence of trauma.

The majority of cases of hemoperitoneum in the general population are gynecologic in origin[15] and this must be considered in cirrhotic, as well as noncirrhotic, females. Careful history and physical examination are essential. The relatively rapid enlargement of the abdomen in hemoperitoneum is in contrast to the slow accumulation of cirrhotic ascites. Abdominal x-rays and biochemical analysis of serum and abdominal fluid should exclude ischemic bowel disease, perforated viscus and pancreatitis. The usefulness of angiography in evaluating hemoperitoneum in a cirrhotic has been questioned[21] and it is true that in the two cases in which it was performed, it failed to establish the diagnosis. We believe, however, that selective abdominal arteriography should be performed, if time and institutional expertise permit, to exclude other insults to which alcoholics and cirrhotics are predisposed, e.g. intra-abdominal trauma and ruptured hepatocellular carcinoma. In the general population, more than 20% of cases of hemoperitoneum are clearly related to trauma.[15] This figure is likely to be higher among alcoholics. In addition to identifying splenic rupture and localizing traumatic arterial bleeding elsewhere, selective arteriography can establish or exclude a diagnosis of hepatic or small bowel tumor, arteriosclerotic (particularly nonaortic) aneurysm and inflammatory erosion of the cystic or appendiceal artery. Negative angiographic studies in the present case suggested a venous bleed.

The present report brings to eight the number of cases of ruptured intra-abdominal varices in the literature. All were cirrhotic, although this is almost certainly a reflection of the marked prevalence of cirrhotic versus noncirrhotic portal hypertension and does not suggest any differences in varix pathogenesis or prognosis. The fact that all eight patients were male is probably also coincidental and there is no reason to believe that being female affords any protection from developing this complication of cirrhosis. Except for one patient who died before surgery could be performed, in each case the diagnosis of bleeding intra-abdominal varices was made at laparotomy. Deserving emphasis is the clinical presentation, which was identical in all cases—sudden onset of increasing abdominal distention (often accompanied by diffuse abdominal pain), tachycardia and hypotension. Six of the eight patients failed to survive. One rapidly exsanguinated and the diagnosis was established at postmortem. Of the five who died despite correct diagnosis and appropriate surgery, four deaths were directly attributable to hepatic failure with generalized bleeding diathesis, progressive encephalopathy and/or compromised renal function. One patient died postoperatively from complications of esophagogastric variceal hemorrhage.

Paracentesis established the presence of hemoperitoneum. The only definitive therapy for rupture of an intra-abdominal varix is operative exploration with plication of the bleeding vessel. Whether this should be coupled with portasystemic anastomosis is unknown but once the diagnosis of a bleeding intra-abdominal varix has been made, the patient's remaining hepatic function and ability to withstand surgery are probably most important in determining ultimate prognosis.

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***Clinical Vignette***

# Ascending Colon Volvulus Due to a Vitelline Duct Remnant in an Elderly Patient

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A 77-year old female is presented with volvulus of the ascending colon due to torsion around a vitelline duct remnant. Symptoms were mild and intermittent. Roentgenograms are presented which demonstrated this lesion preoperatively. At surgery the ascending colon was found to be twisted around a fibrous band extending from the umbilicus to the ileum.

Volvulus, caused by torsion of bowel around remnants of the vitelline duct, is an uncommon cause of bowel obstruction. Most cases occur in a pediatric population and the diagnosis is not often considered in older patients. We present an septuagenarian who presented with a one-year history of intermittent vague abdominal complaints which were subsequently shown to be caused by intermittent volvulus of the ascending colon due to a fibrous band formed from an vitelline duct remnant.

## Case Report

A 77-year old female was admitted with a one-year history of intermittent episodes of abdominal bloating, crampy abdominal pain and nonfeculent vomiting which would last from one to three days. In the intercurrent periods she was asymptomatic. A barium enema, obtained ten months prior to admission (Fig. 1), showed an anomalous position of the cecum and ascending colon in the upper abdomen. No evidence of obstruction was present but marked redundancy of the colon was noted. A repeat barium enema, obtained during an episode of abdominal discomfort five months prior to admission (Fig. 2), showed partial obstruction from torsion of the ascending colon. The cecum and ascending colon, proximal to the twisted area, appeared to be rotated and displaced downward from its previous location in the upper abdomen. This episode resolved spontaneously and surgery was not done due to the patient's advanced age. In the subsequent five months prior to admission the episodes of abdominal distress became more frequent and severe and she was admitted to the hospital for evaluation. She had lost 2.7 kg. in the month prior to admission. She had no history of abdominal surgery or serious medical illness and was on no medications.

Physical examination showed an elderly female in minimal distress with blood pressure, 120/80; heart rate, 90 and temperature, 37.1° C. Abdominal examination

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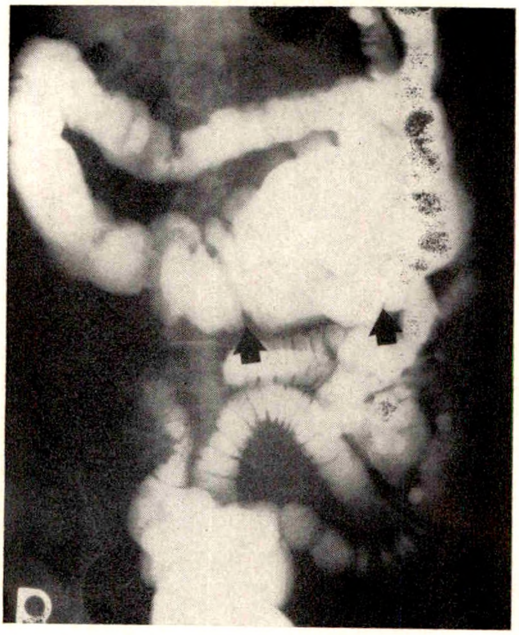

Fig. 1—Barium enema obtained 10 months prior to admission shows the ascending colon and cecum located in the upper abdomen (arrows). Marked redundancy of the colon is also present.

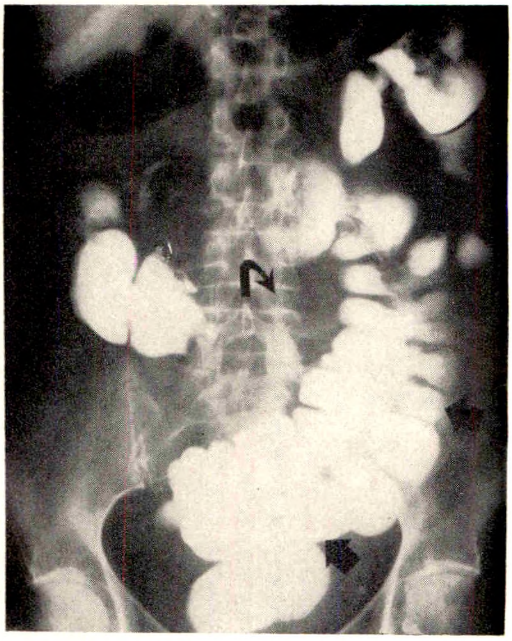

Fig. 2—Barium enema five months prior to admission shows retention of barium in the ascending colon and cecum proximal to a partial volvulus (arrows) with the torsion occurring in the mid abdomen (curved arrow).

revealed normal bowel sounds and mild tenderness in the right lower quadrant. There were no palpable masses and the stool was occult negative. Laboratory studies showed a Hg., 13.3 gm.; Hct., 39.9%; WBC, 5,800 with 60 neutrophils, 28 lymphocytes, 10 monocytes and 2 eosinophils. Serum electrolytes, BUN, albumin, SGOT, alkaline phosphatase and blood sugar were normal. Roentgenologic abdominal films were normal with no air fluid levels or dilated bowel present. A barium enema showed complete obstruction of the ascending colon with a hook-like tapering tip suggestive of volvulus located in the mid abdomen (Fig. 3). An upper gastrointestinal series (Fig. 4) again demonstrated the area of torsion in the mid abdomen and the pelvic position of the cecum and ascending colon proximal to the twisted area. Barium did pass antegrade and it appeared that the volvulus was occurring around a fixed structure in the mid abdomen.

Surgical exploration demonstrated a fibrous band which measured 1.3 cm. in greatest diameter extending from the umbilicus to the ileum. A Meckel's diverticulum was not found and there were no fibrous bands coursing through the mesentery. The ascending colon was wrapped around the band resulting in a volvulus. After removal of the fibrous band the volvulus was easily reduced and the cecum placed in the right lower quadrant of the abdomen. At surgery the colon was noted to be very redundant. Following surgery the patient recovered uneventfully and has had no recurrence of symptoms. A postoperative barium enema showed the cecum to be located in the normal position.

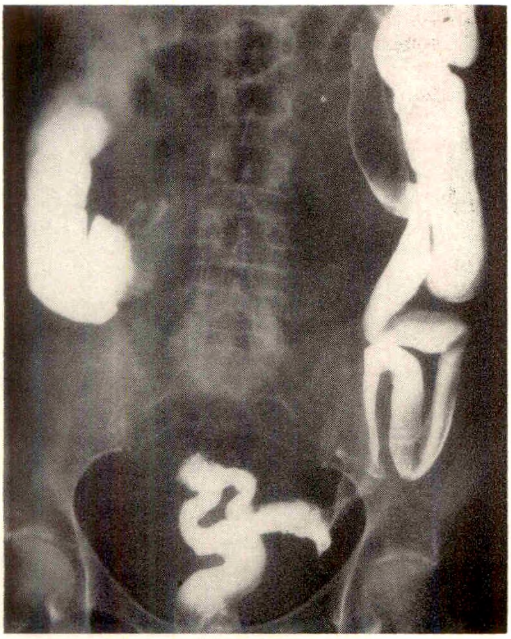

Fig. 3—Barium enema obtained on admission which shows complete obstruction in the ascending colon with the column of barium terminating in the mid abdomen in a configuration suggestive of volvulus.

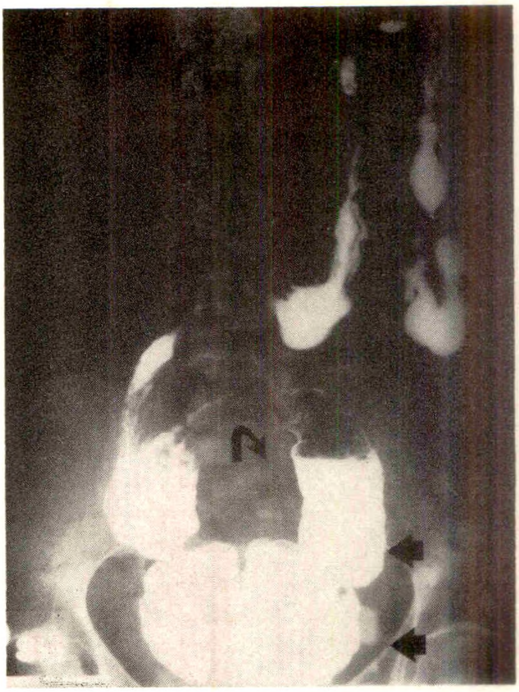

Fig. 4—Late film from an upper gastrointestinal series demonstrating volvulus in the mid abdomen (curved arrow) and location of the ascending colon and cecum in the pelvis (short arrows).

## COMMENT

Bowel obstruction due to volvulus around a vitelline duct remnant is most frequently encountered in a pediatric population. Our patient is unusual in that she did not have symptoms related to her developmental defect until she reached an advanced age. Even then symptoms were intermittent and mild. Due to this mildness and the tendency for spontaneous resolution several months passed before the source of her problem was elucidated. Redundancy of the colon, or dolichocolon, which she exhibited is often associated with constipation and an older age group. Dolichocolon may be associated with increased colon mobility. This could account for the delay in onset of symptoms until an advanced age.

The vitelline duct is a portion of the embryonic yolk stalk which usually atrophies in the second month of gestation. Failure of the duct to close properly may produce an umbilicoenteric fistula, an umbilical sinus (patency of the peripheral portion of the duct); a vitelline cyst (closed remnant of the mid portion of the duct), a Meckel's diverticulum (patency of the proximal portion of the duct) or a fibrous band extending from the umbilicus to the ileum, most commonly to the antimesenteric border.[1, 2]

In addition to persistent vitelline duct remnants, fibrous bands can result from remnants of the vitelline arteries or veins.[3-5] The first reported case of small bowel obstruction due to a vitelline vascular remnant dates to 1777.[6] Reports of this condition have been infrequent. Prust and Abouatme identified only 28 cases in the literature prior to 1969.[4] Moore noted that a nonstrangulating type of obstruction seems to result from volvulus of the bowel around a fibrous cord attached to the umbilicus and is associated with low surgical mortality. On the other hand, internal hernias resulting from attachments from the ileum to adjacent mesenteric structures, such as may occur with some vitelline vascular remnants, have higher surgical mortality.[7] Only careful examination of the origins of these bands allows differentiation from a persistent vitelline duct structure. Fibrous bands resulting from vitelline vein remnants usually course through the ventral mesentery from the umbilicus to the infraduodenal area near the portal vein. Since vitelline artery remnants are most commonly atrophied extensions of the superior mesenteric artery, remnants of this vessel usually pass through the mesentery to the area of the terminal end of the superior mesenteric artery. As in obstruction from vitelline duct remnants, this usually occurs in a pediatric population.

Fibrous bands resulting from vitelline duct and vitelline vascular structures are usually discovered at laparotomy, however, nitrous oxide pneumoperitoneography has been used successfully for noninvasive diagnosis in selected cases.[8]

The findings demonstrated by this case should alert physicians to consider vitelline duct or vitelline vascular remnants as an uncommon cause of bowel obstruction even in elderly patients.

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***Clinical Vignette:***

# Caroli's Disease

## Description of a Rare Clinical Case with Monolobar Localization

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A case of monolobar localization of Caroli's disease with intrahepatic cholesterol gallstones is described.

The patient was successfully treated with left hepatic resection. Residual intrahepatic cholesterol gallstones causing frequent cholangitis dissolved with chenodeoxycholic acid treatment.

Cystic dilatation of intrahepatic common bile ducts, or Caroli's disease,[1, 2] generally affects the whole hepatic parenchyma. It is characterized by a cystic ectasia of the intrahepatic bile ducts which form a network of communicating cavities with the main bile duct, intrahepatic biliary lithiasis and recurring cholangitis in a moderately enlarged liver. It is often associated with renal disease, i.e. medullary cystic spongiosis (Cacchi and Ricci's disease),[3] is probably linked to an autosomal recessive inheritance and seems to be more frequent in males.

Two varieties of the disease are described by Caroli: the pure form and the form associated with periportal fibrosis.[2]

According to some authors,[4, 5] Caroli's disease differs considerably from other polycystic diseases of the liver inasmuch as in the latter there is a higher incidence in women and a marked difference in the modality of transmission (autosomal dominant gene), clinical aspects (hepatomegaly, absence of cholangitis, polycystic kidney) and liver morphology (several cysts non-communicating with bile ducts, containing mucus).[4-6]

The differences between Caroli's disease and congenital hepatic fibrosis, however, appear less distinct since the anatomopathological findings and inheritance are similar. Congenital hepatic fibrosis is frequently associated with medullary and cortical renal tubular ectasia; on the other hand congenital hepatic fibrosis often causes a presinusoidal portal hypertension syndrome.[7, 8]

In the present report a rare clinical case of monolobar segmentary ectasia of the intrahepatic biliary tree is described and fol-

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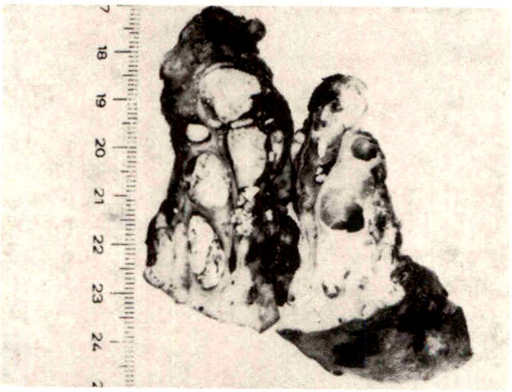

Fig. 1—Abnormalities of the intrahepatic biliary system: cystic dilatations and cyst-like gallstones are visible.

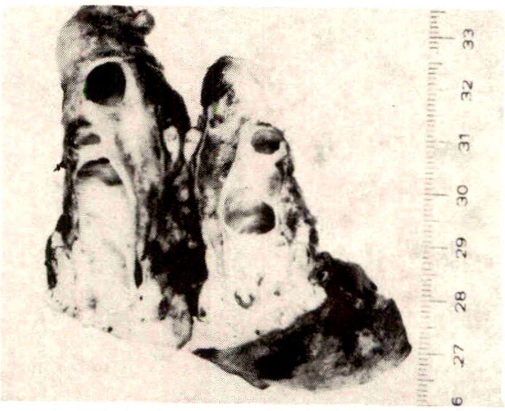

Fig. 2—Same as Figure 1 without stones.

low-up and surgical and medical treatment are discussed.

## Case Report

A 45-year old male, G. A., was admitted to the General Hospital of Prato, Surgery Division, with severe abdominal colic.

The family and clinical histories were negative.

The patient had followed a hyperglycideremic and hypercaloric diet with a daily consumption of approximately one liter of wine until the age of 37.

He reported moderate constipation. Diuresis was normal. The medical history was uneventful up to age 38. At that time, the patient had several episodes of crampy pain in the right upper abdomen. The symptoms had resolved spontaneously and the patient had not sought medical advice. At the time he was 20 kg., overweight. Upon admission the patient had a three months' history of frequent and increasing abdominal pains with loss of weight, nausea, anorexia and intolerance to fats. An episode of bilioseptic fever was also reported.

On no occasion had he noticed the presence of mild jaundice, or of hyperchromic urine, alcoholic feces or pruritus. The patient was slightly overweight. The physical examination revealed pain in the upper right hypochondrium area, positive Murphy test and an enlarged liver, severe asthenia and nausea; the spleen was not palpable.

The laboratory tests performed upon admission indicated normal blood morphology, nitrogen content, serum protein, urine, bilirubin, alkaline phosphatases and amylases. X-ray examinations and electrocardiogram were also normal. Blood group was A Rh positive.

I.V. cholangiography failed to show the intra- and extrahepatic bile ducts. Diagnostic laparotomy revealed several gallstones in the gallbladder which showed signs of pericholecystitis and a 10 cm. area characterized by superficial ectasic bile duct aggregates, half way in the left liver lobe, probably filled with stones. The remainder of the liver had a normal appearance.

The impaired parenchyma was removed and cholecystectomy carried out. Intraoperative cholangiography showed a normal common bile duct.

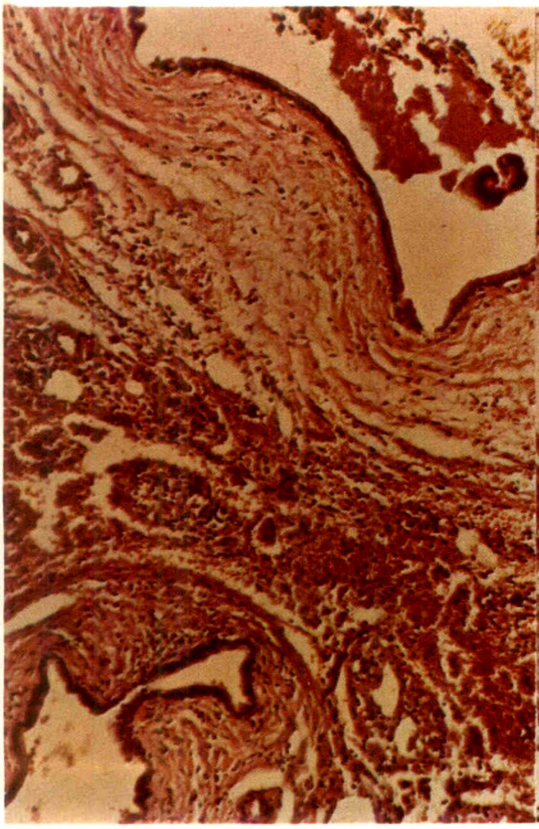

Fig. 3

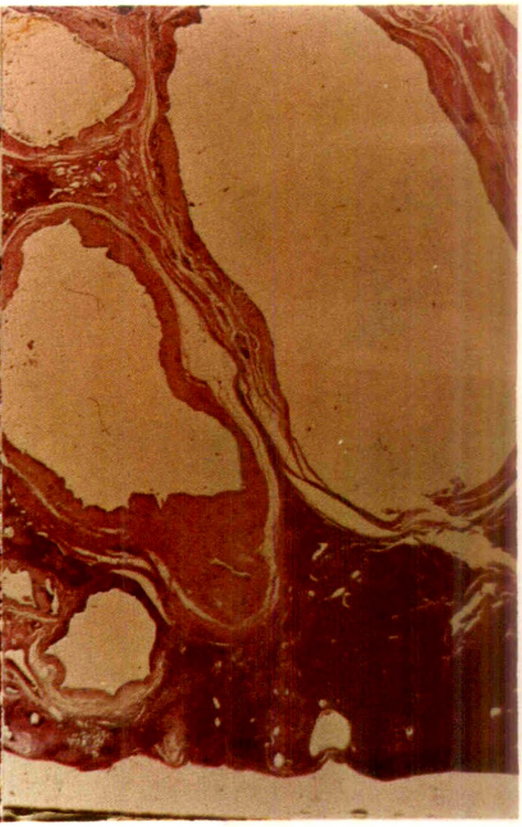

Fig. 4

Fig. 3—Large dilated bile duct with bile and dead epithelial cells of the bile duct in the lumen.

Fig. 4—Group of cysts lined with endothelial cells.

The gross specimen showed communicating cystic dilatation containing a negligible amount of bile and very large cyst-like stones (Figs. 1 and 2).

Chemical analysis revealed that the stones were composed predominantly of cholesterol (70%), like those found in the gallbladder. Histological pattern of the tissue removed presented a network of large cavities of various sizes, covered by a single-layer of cylindrical epithelium often filled with bile (Fig. 3).

Also visible were a few cavities of a different type which appeared empty. These cavities were covered by endothelial-like cells, surrounded by either connective-muscular tissue or connective tissue (Fig. 4).

Similar smaller sized aggregated cavity-like formations, with a large amount of connective tissue and slight lymphocyte infiltrations were observed in occasional scattered areas.

There were no postoperative complications. The patient was discharged 20 days after surgery with a diagnosis of intrahepatic and cholecystic lithiasis. Two months later a liver scan (Fig. 5) with colloid gold ($^{198}$Au) revealed a normal radiocolloid distribution and normal conformation of the hepatic parenchyma. Al-

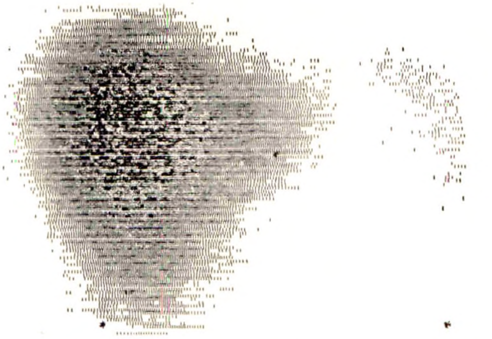

Fig. 5—Normal liver scintigram two months after liver resection.

though the patient continued his normal activities he complained in the following months of asthenia, pain in the right hypocondrium, intolerance to fats.

Every four or five months biliary colic occurred, characterized by chills, high fever and increased alkaline phosphatases. These colics were successfully treated with antibiotic therapy. In spite of persistence of the symptoms the patient refused other treatment for about four years.

In October 1975, the patient was admitted to the Gastroenterological Unit of St. Orsola Hospital in Bologna, for a more severe colic attack. Physical examination revealed a slight enlargement of the liver 2 cm. below the right costal margin. The spleen was not palpable. Laboratory tests revealed normal transaminases, alkalines phosphatases, cholesterol, prothrombin time, serum lipoproteins, triglycerides, serum immunoglobulins (Ig-G, Ig-A, Ig-M) and nonorgan-specific antibodies.

Barium examination of the gastrointestinal tract and the I.V. pyelogram were also normal.

Transpapillary cholangiography revealed a hemispheric papilla located at the upper third of the descending duodenum, normal in appearance and easily cannulated.

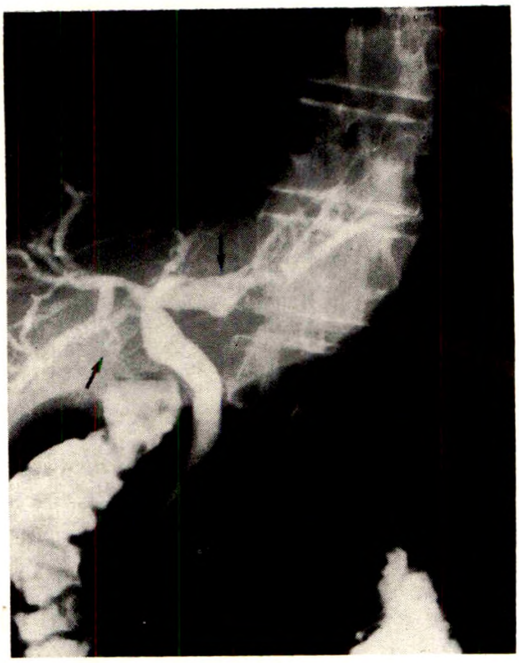

Fig. 6—X-ray of ERCP demonstrates two medium sized radiolucent stones in the left duct and a small radiolucent stone in an ectasia of right duct (arrows).

After injection of 30 ml. of contrast medium, the following observations were made: 1. the extrahepatic bile ducts had a normal appearance without stones, with a filiform terminal choledochus and with a rapid emptying (30 minutes); 2. The intrahepatic bile ducts were clearly visualized as far as the smallest ducts. The left intrahepatic duct showed a slight ectasia with three radiolucent stones (Fig. 6) and a small stone in the presence also of ectasia of the right hepatic duct (see arrow).

Lipid composition of a choledochus bile sample[9, 10] taken at the beginning of the examination was as follows: (mol %): cholesterol, 11%; phospholipids, 23%; bile salts, 66% and saturation index, 1.6, i.e. supersaturated in cholesterol.[9, 10]

Wedged hepatic vein pressure was normal, thereby excluding portal hypertension. Thus, taking into account the cholesterol

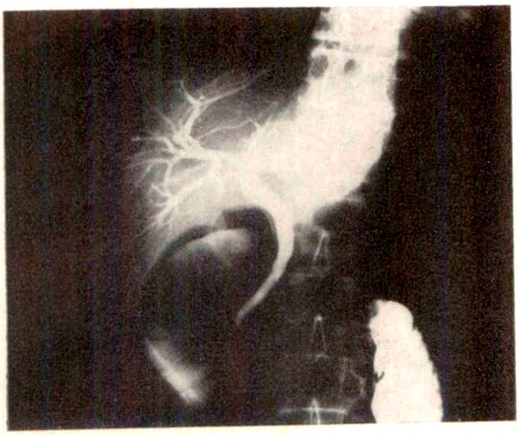

Fig. 7—X-ray of ERCP shows complete disappearance of cholesterol gallstones.

gallstones previously removed, the radiolucency of the present stones, the bile supersaturated in cholesterol and the difficulties in performing another operation it was decided to administer chenodeoxycholic acid 15 mg./kg./day.[11-13]

After six months of treatment the bile was less saturated (S.I., 1.01; cholesterol 6.1%; phospholipids, 19.7%; bile acids 74.2%). The clinical picture also showed improvement. Transpapillary cholangiography showed complete disappearance of cholesterol gallstones (Fig. 7).

## COMMENT

The clinical history of the patient, the surgical findings of cystic dilatations of intrahepatic bile ducts filled with bile and stones and the absence of portal hypertension, contribute to the diagnosis of Caroli's disease.

Several observations must be made concerning the singularity of the case: 1. The exceptional localization of the disease in a limited tract of the hepatic parenchyma; only two cases have so far been described in the literature;[14, 16] 2. the presence of other nonbiliary cystic dilatations such as those observed in congenital hepatic fibrosis; 3. the absence of renal abnormalities; 4. the normal regeneration of the parenchyma removed; 5. the presence of cholesterol stones; calcium bilirubinate stones have already been found in cases of Caroli's disease.[1]

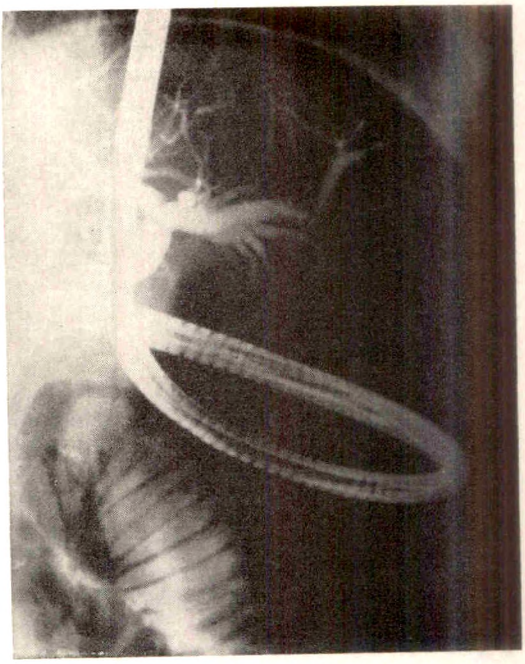

Fig. 8—Detail of the left intrahepatic biliary tree without stones.

The case described reopens the discussion regarding the problem of the nosographic setting of the disease. Some authors[16, 17] group Caroli's disease, congenital hepatic fibrosis and polycystic diseases of the liver together. Others[7, 18] distinguish the first two diseases from the latter and we are in agreement with this distinction because of the different mode of transmission, the presence of noncommunicating cysts with the common bile duct and the rarity of portal hypertension in the latter group of diseases.

The histological pattern of Caroli's disease and congenital hepatic fibrosis, on the other hand, seems to be more closely related and in this respect some authors[7] consider Caroli's disease as an anatomoclinical form of congenital hepatic fibrosis.

In conclusion, prognosis of the disease is not necessarily bad, especially if surgical resection is possible.

Furthermore, since intrahepatic lithiasis may be of the cholesterol type, it may be worthwhile employing chenodeoxycholic acid as a dissolving agent.

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# The Radiology Corner*

## MALIGNANT CARCINOID OF THE APPENDIX: CASE REPORT WITH RADIOGRAPHIC AND ANGIOGRAPHIC DEMONSTRATION

SUSAN L. GOLDFINE, M.D.†
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and
EMIL J. BALTHAZAR, M.D., F.A.C.G.‡
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An unusual case of a malignant carcinoid of the appendix is reported, together with a brief review of the pertinent literature. The case exhibited mesenteric invasion, peritoneal seeding, terminal ileal ischemia and features of the carcinoid syndrome. The radiographic and angiographic documentation are unique in the literature.

The pathologic and clinical features of appendiceal carcinoids have been extensively analyzed in the recent literature.[1-5] For many years, they have been considered interesting pathologic curiosities accidentally discovered during elective or incidental appendectomies and devoid of clinical significance. They are usually small tumors, entirely localized at the appendix, exhibiting a benign course and an excellent clinical prognosis. In the last 20 years, however, several case reports and review articles in the surgical literature have documented unusual cases of malignant appendiceal carcinoids, some of them presenting with widespread metastases.[6-10] To the best of our knowledge, there are no similar cases reported in the radiologic literature and none with radiographic and angiographic illustrations. Such a case is presented and illustrated in the following report.

## CASE REPORT

A 77-year old male was admitted with the history of several weeks of abdominal pain, associated with severe flushing of the upper trunk and face. Lower abdominal tenderness was elicited on physical examination. Laboratory examinations were unremarkable except for repeatedly elevated blood serotonin levels (up to 763 ng./ml.).

On radiographic gastrointestinal study an extraluminal mesenteric mass was visualized in the right lower quadrant (Fig. 1). A superior mesenteric angiography subsequently performed is illustrated in Figure 2. At laparoscopy several small peritoneal nodules were identified. Biopsy of one of the nodules revealed malignant metastatic carcinoid. The patient was discharged on chemotherapy.

The patient continued to complain of episodes of flushing, associated with abdominal pain. Four weeks later he developed fever, diffuse abdominal tenderness, nausea and vomiting for which he was readmitted to the hospital.

---

* Edited by Richard H. Marshak, M.D., F.A.C.G. and Arthur E. Lindner, M.D., F.A.C.G.

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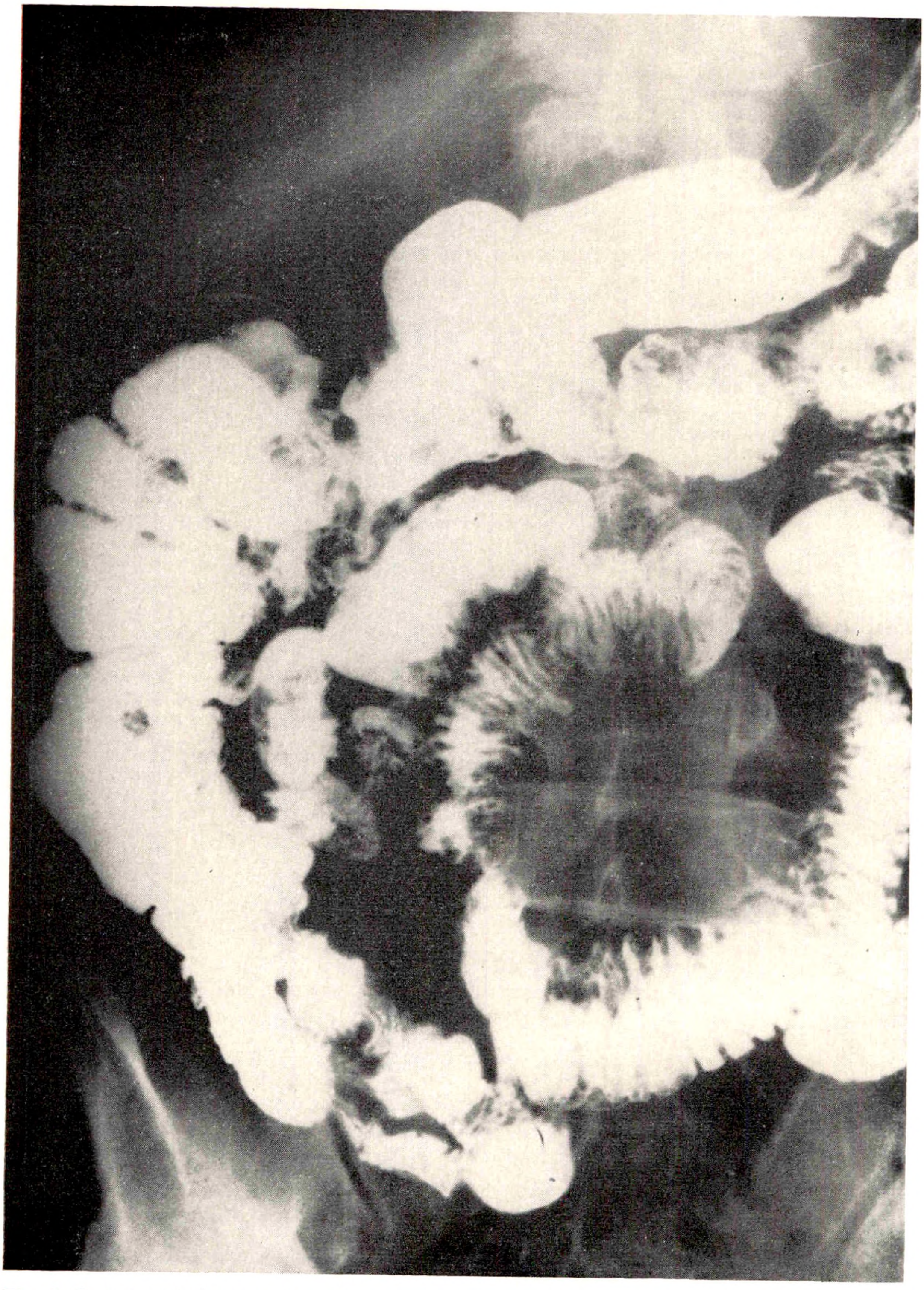

Fig. 1—Gastrointestinal examination demonstrates separation of loops with external compression and moderate spiculation of the terminal ileum by a mesenteric mass.

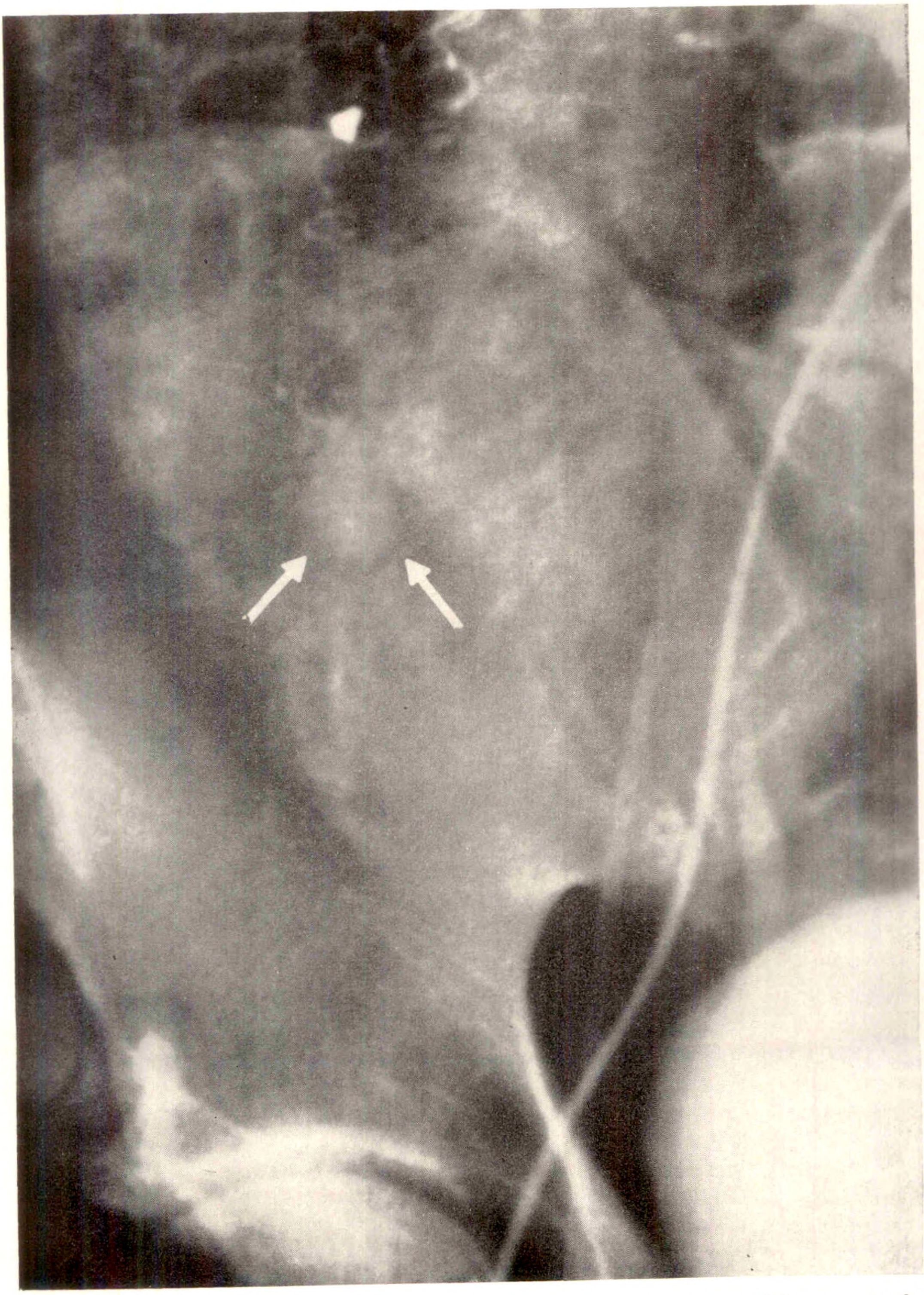

Fig. 2—Capillary phase of the superior mesenteric angiogram reveals a faint stain of the tumor in the right lower quadrant (arrows).

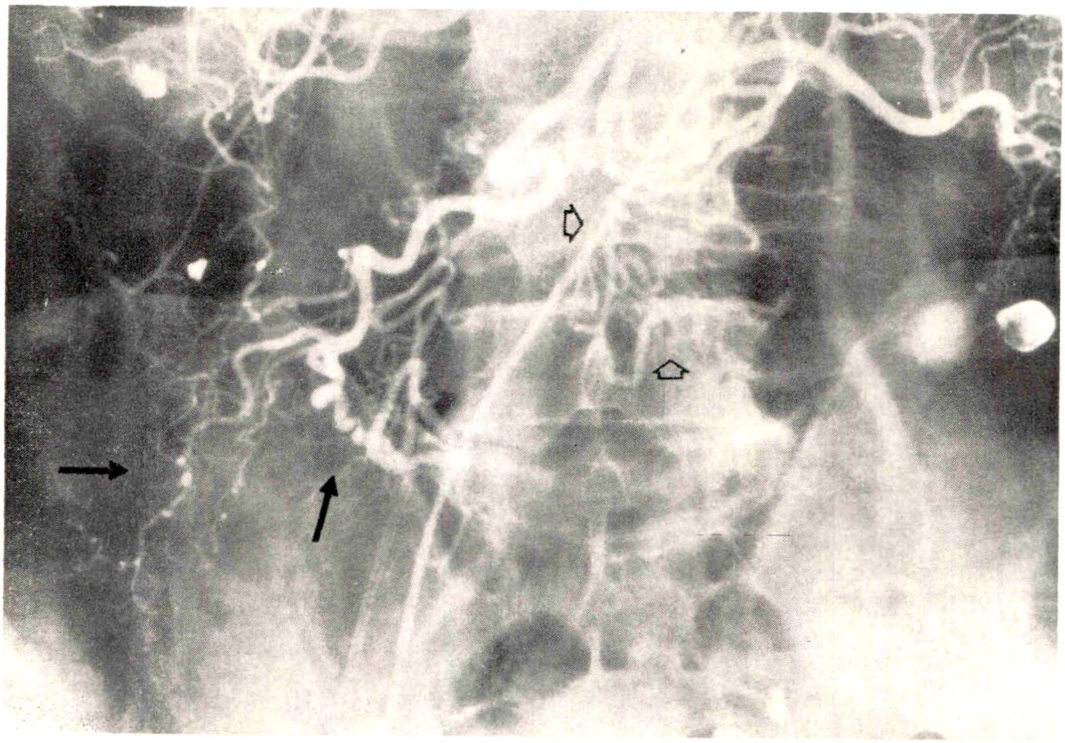

Fig. 3—Superior mesenteric angiography, arterial phase, shows irregular narrowing and kinking of the intermediate and smaller branches of the ileocolic artery visualized in the right lower quadrant (arrows). Localized encasement with a stellate pattern of the more central mesenteric branches is visualized (open arrows).

Physical examination revealed rebound tenderness throughout the abdomen and an emergency laparotomy was performed. Multiple peritoneal seedings and a mass in the right lower quadrant were visualized, containing 30 cm. of gangrenous terminal ileum. A right hemicolectomy and a terminal ileal resection were performed.

Examination of the pathologic specimen showed a carcinoid tumor arising from the appendix, infiltrating the mesentery and the regional lymph nodes by extension. The tip of the appendix could not be identified because of the infiltrating periappendicular mass. The terminal ileum was gangrenous and multiple firm white nodules, measuring an average of 0.4 cm. were present on the serosal surface. The patient had a stormy postoperative course but subsequently recovered and was discharged on chemotherapy.

## COMMENT

Appendiceal carcinoids represent the most common tumors of the appendix. The appendix is the most common site of gastrointestinal carcinoids.[1, 2] The surgical rate of occurrence varies depending mainly on the diligence of pathologic search, with figures between 0.1-0.7% quoted in the literature.[1, 2, 11] Although recognized at any age, they are generally found in younger patients within the second, third and fourth decades, while the peak incidence of other carcinoids is above the fifth decade.[1, 2, 12]

The increased incidence in women (about three to one) is sometimes explained by the frequency of pelvic operations associated with incidental appendectomies.[1-5] Appendiceal carcinoids may coexist with other carcinoids of the gastrointestinal tract, or in 20-30% of the cases, with other malignant tumors.[2, 3] On gross examination, they present as localized nodules of firm to rubbery consistency and yellowish-tan in color. They may obstruct the lumen presenting as appendicitis. In about 70% of the cases, they measure less than 1 cm. in size and are located at the tip of the appendix.[2, 4, 6] Histologically, they may be confined to the submucosa although often, mural invasion is recognized.[1-5, 13] There is still controversy as to the meaning of muscular and even serosal invasion, since there is no good correlation between these histological features and the presence of metastases. It has been repeatedly shown that a simple appendectomy in the presence of intramural invasion represents the proper treatment, without the development of local recurrency or metastatic disease on long follow-up examinations.[1, 2, 4, 5] On the other hand in the presence of lymphadenopathy, mesenteric or cecal invasion and/or primary tumors larger than 2 cm. in size, wide resections with hemicolectomies are recommended.[2-4] There have been only about 40 cases of malignant carcinoids that exhibited regional or distant metastases at the time of the diagnosis.[1, 2, 6-10, 14, 15] Among the appendiceal carcinoids, the incidence of metastasizing lesions is about 2%.[3] The criteria for malignancy should include the presence of metastases (common within the regional lymph nodes) while excluding the existence of a secondary primary, particularly of the ileum, that may be responsible for the metastatic disease.[13] If the development of metastases secondary to appendiceal carcinoids is an uncommon occurrence, the association of a carcinoid syndrome is extremely rare. There have been only four cases reported and quoted in the literature, all of which demonstrated liver metastases.[1, 2, 8]

The case presented in this report exhibited highly unusual and even unique features. It represents a case of an appendiceal carcinoid with documented mesenteric invasion and peritoneal seeding and it fullfills the criteria of malignancy mentioned above. It is one of a handful of cases of appendiceal primary lesions with associated features of the carcinoid syndrome. Liver metastases was not documented in our case but could not be completely excluded since a thorough examination of the liver was not performed. The unique features of this case pertain to the development of ileal ischemia and necrosis as a consequence of mesenteric invasion and vascular compromise, as well as to documentation of regional metastases by radiographic and angiographic means.

The radiographic findings were those of a mesenteric mass with separation of loops, external compression, asymmetrical spiculated contour and intestinal kinking (Fig. 1). These features were not unlike those previously described with malignant carcinoids of the ileum.[16-18] The angiographic findings were quite characteristic and again similar to the findings observed with malignant ileal carcinoids.[19, 20] There was faint staining in the right lower quadrant, probably within the primary lesion and its adjacent mesenteric infiltrating mass (Fig. 2). There was, in addition, irregular narrowing and kinking of the smaller branches of the ileocolic artery and the distal mesenteric arcade as well as local encasement with a stellate pattern to the more central mesenteric branches. This is presumably the result of mesenteric fibrosis with foreshortening (Fig. 3). These radiographic and angiographic features have never been described or illustrated in association with a primary appendiceal carcinoid.

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# The Last Page

## QUESTIONS IN GASTROENTEROLOGY

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**New York, N. Y.**

*The Last Page* appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the article can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. ELEVATED AMYLASE IN ACUTE ALCOHOLISM:
   - A. Elevated serum or urinary amylase was found in one-third of unselected patients with acute alcoholic intoxication.
   - B. Pancreatic or "P"-type amylase was more often elevated than salivary or "S"-type.
   - C. Most patients who had an elevated amylase clearance/creatinine clearance ratio had hyperamylasemia.
   - D. "S"-type isoamylase originates only in the salivary glands.

   (Page 557)

2. EARLY GASTRIC CANCER:
   - A. Is defined as carcinoma limited to the mucosa and submucosa.
   - B. Has a five-year survival rate of 85-90% when resected early.
   - C. Is often multicentric.
   - D. Type I (protruded) and Type II (superficial) are harder to diagnose by biopsy than Type III (excavated).

   (Page 563)

3. ENDOSCOPIC ELECTROCOAGULATION AND UPPER GASTROINTESTINAL BLEEDING:
   - A. Is inexpensive and utilizes commercially available electrocoagulator and unipolar electrode.
   - B. Is less effective on a wet surface.
   - C. Histologic features include coagulative necrosis of mucosa and occlusion of mucosal and submucosal vessels.
   - D. Esophagus and duodenum are less resistant than stomach to the effects of electrocoagulation.

   (Page 568)

4. DIALYSIS CLEARANCE OF CIMETIDINE IN RENAL FAILURE:
   - A. Peptic ulcer and upper gastrointestinal bleeding in renal failure are best treated medically with magnesium-containing antacids.

---

[*] Associate Professor of Clinical Medicine, New York University School of Medicine.

B. Hemodialysis clearance of cimetidine was found to be 40-75 ml./min.

C. Peritoneal dialysis clearance of cimetidine is greater than with hemodialysis.

D. The amount of cimetidine removed by peritoneal dialysis is still only a small fraction of the total dose.

(Page 572)

5. GASTRIC IRRADIATION FOR PEPTIC ULCER:

A. Was used for intractable peptic ulcer disease in patients who were poor surgical risks.

B. Involves daily irradiation of anterior and posterior fields to a total of 2,000 rads.

C. Although maximal histamine-stimulated acid secretion tended to return to pretreatment levels after irradiation, basal secretion remained lower.

D. Long-term results are very good with recurrence in under 10%.

(Page 577)

6. HEPATIC BRUITS:

A. May be heard in hepatoma and alcoholic hepatitis.

B. Are continuous, with or without systolic accentuation.

C. Do not occur with metastatic malignancies or cholangiocarcinoma.

D. Are due to hepatic artery/portal vein shunting.

(Page 582)

7. ADH AND THE PANCREAS:

A. ADH decreases basal and secretin-stimulated exocrine flow.

B. ADH reduces pancreaticoduodenal blood flow.

C. ADH does not modify experimental pancreatitis when given before or after its onset.

D. Acute hemorrhagic pancreatitis does not reduce the sensitivity to secretin.

(Page 587)

8. CROHN'S DISEASE OF THE APPENDIX:

A. The appendix is often the primary site of Crohn's disease.

B. When the appendix is the primary site, appendectomy is never followed by fistula.

C. Fecal fistula after appendectomy in Crohn's disease usually arises in the remaining diseased bowel.

D. Postoperative total parenteral nutrition may prevent or heal fecal fistula in such cases.

(Page 592)

9. METASTATIC TUMOR TO THE STOMACH:

A. Primary tumor may be in the lung, breast, pancreas or colon,

B. Melanoma may metastasize to the stomach in as many as 20% of such cases.

C. Metastases are often polypoid lesions with central umbilication or ulceration.

D. No other gastric lesions present as umbilicated polyps.

(Page 598)

10. EXTRAMEDULLARY PLASMACYTOMA OF THE STOMACH:

A. Is as common as in the respiratory tract or conjunctiva.

B. Is always a secondary feature of multiple myeloma.

C. Shows large dilated and tortuous vessels on angiography.

D. Is usually treated by surgery with radiation or chemotherapy.

(Page 601)

11. TRAUMATIC HEMOBILIA:

A. Causes intermittent right upper quadrant pain, fluctuating jaundice and acute upper gastrointestinal bleeding, usually after a long latent period.

B. Oral cholecystography and IVC reveal radiolucent defects, that appear as echo-free areas on sonography.

C. ERCP reveals bleeding from the papilla.

D. Arteriography is not necessary before surgery.

(Page 605)

12. RIEGER'S SYNDROME:

A. This is a combination of hypodontia with malformation of the anterior eye chamber.

B. Associated anomalies include anal stenosis and renal malformation.

C. Meckel's diverticulum is commonly associated with this syndrome.

D. $^{99}$Tc pertechnate isotope scanning will always reveal Meckel's diverticulum.

(Page 608)

13. INTRAPERITONEAL VARICEAL RUPTURE IN CIRRHOSIS:

A. In addition to the esophagogastric area, other sites of variceal bleeding in cirrhosis are the small and large bowel and rectum, vagina, ileostomy and colostomy stomas and postoperative adhesions.

B. Most common causes of hemoperitoneum in the general population are gynecologic and trauma.

C. Hemoperitoneum due to variceal rupture results in only slow abdominal distention.

D. Angiography will identify variceal bleeding and distinguish it from trauma, hepatoma or other tumor.

(Page 611)

14. VOLVULUS AROUND A VITELLINE DUCT REMNANT:

A. Failure of the vitelline duct to atrophy may leave an umbilicoenteric fistula, an umbilical sinus, a vitelline cyst, a Meckel's diverticulum, or a fibrous band.

B. Volvulus around it never occurs in an adult.

C. Other vitelline structures, such as arteries or veins, may also form bands.

D. Pneumoperitoneography may reveal these bands.

(Page 617)

15. CAROLI'S DISEASE:

A. Consists of cystic dilatations of the intrahepatic bile ducts, intrahepatic gallstones and recurring cholangitis.

B. Is the same as polycystic disease of the liver.

C. Is often associated with medullary sponge kidney.

D. Is always generalized, involving both lobes of the liver.

(Page 621)

16. APPENDICEAL CARCINOID:

A. This is the most common of the gastrointestinal carcinoids and is usually small, localized and benign.

B. It is frequently associated with the carcinoid syndrome.

C. It shows a tumor stain on angiography, with irregular narrowing, kinking and encasement of arteries with malignant carcinoid.

D. Simple appendectomy is adequate even in the presence of lymphadenopathy, mesenteric or cecal invasion, or of tumor size greater than 2 cm.

(Page 627)

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# BOOK REVIEWS FOR GASTROENTEROLOGISTS

**Annual Review of Medicine: Selected Topics in the Clinical Sciences Vol. 29, 1979: edited by W. P. Creger. 614 pages, illustrated. Annual Reviews Inc., Palo Alto, CA, 1978. Price $17.00.**

For the price, the Annual Review of Medicine, 1978, is a bargain. The contributors to the various monographs read like a "Who's Who of Medicine". The articles are written by prominent teachers and practitioners, frequently with "associates" in their departments.

There is little in the field of gastroenterology that has not been discussed in recent journal articles and other reviews. Notwithstanding, the articles on Acid Secretion, Protein Metabolism, Gastrointestinal Hormones, Non-A, Non-B Hepatitis and the Disposition of Sedatives by Diseased Liver are well done and accompanied by superb bibliographies.

In general, the reviews are somewhat superficial but the bibliographies are up to date and outstanding. I would think this book is designed primarily for the general internist and house officers in Medical Residency programs.

Walter Harvey Jacobs, M.D., F.A.C.G.

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**Education of a Hospital Trustee: Changing Roles for Changing Times: edited by Lewis E. Weeks. 155 pages, illustrated. The W. K. Kellogg Foundation, Battle Creek, MI, 1977.**

This small soft-cover book deals concisely and accurately with the problems facing members of the Boards of Trustees of American hospitals. Much of the information included is derived from a forum on Trustee Education held in Memphis, TN in November, 1976. Great emphasis is placed upon the new responsibilities of hospital trustee members including their legal responsibility for the quality of care provided by the hospital. There is a discussion of auditing of hospital performance such as Professional Activity Study and Medical Audit Programs of the Commission on Professional Hospital Activities and investigations by the Joint Commission on Accreditation of Hospitals.

A particularly important discussion ensues concerning the future of medical care . . . Beautifully stated,—"it isn't the laws that are passed that are the greatest danger, but the regulations that are promulgated to implement the laws, that often are insidious—and should be guarded against". Furthermore, it states that the forum took the position that Boards should defend the rights of hospitals for which they are responsible, to the point of going to court to oppose unfair rules, regulations and laws and to oppose pressure from third parties.

There is adequate discussion of the importance of "new blood" on the Board of Directors and the problems with a self-perpetuating hospital trustee board. Perhaps there is too little discussion dealing with the input of the medical staff to "the Board" and the role of physicians as board members, however, education of Trustees is emphasized and should overcome this one shortcoming.

This book should be made available to all new members of Boards of Trustees as well as Executive Committees of Medical Staffs, so that they can get "a feel" for one another and establish better lines of communications.

Walter Harvey Jacobs, M.D., F.A.C.G.

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**Ultraschalldiagnostik (B-scan) in der Inneren Medizin, Lehrbuch und Atlas: by Harald Lutz, M.D. 152 pages, illustrated. Springer-Verlag, Berlin, Germany, 1978. Price $39.00.**

This book on *Diagnostic Ultrasonography* was written by Harold Lutz of Erlangen, Germany in collaboration with R. Petzoldt and R. Ehler.

The text and illustrations are based on a six-year experience with this remarkable diagnostic tool. Following a general introduction, the technics applicable to various anatomic regions and organs are described and depicted with remarkable accuracy and simplicity.

Clearly, this is a book-atlas combination that will prove valuable not only to sonographists but also to clinicians in many disciplines.

Please note that this book is written in German.

Demetrius Pertsemlidis, M.D., F.A.C.G.

---

**The Kidney in Liver Disease: edited by Murray Epstein, M.D. 374 pages, illustrated. Elsevier North-Holland Inc., New York, NY, 1978. Price $32.50.**

The renal abnormalities complicating advanced liver disease are the focus of this book co-authored by 42 contributors and edited by Murray Epstein of Miami, FL. The international and multidisciplinary representation of the contributors is a reflection of the importance of the subject that transcends national and medical specialty barriers.

The chapters of volume regulation, sodium and water handling, the renin-angiotensin-aldosterone system, the prostaglandins and kinins and finally the section on therapeutics are written with precision and clarity.

The book is valuable to nephrologists, hepatologists and general surgeons.

Demetrius Pertsemlidis, M.D., F.A.C.G.

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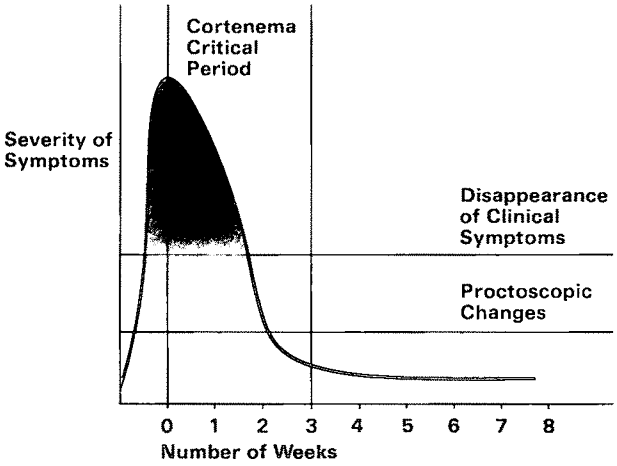

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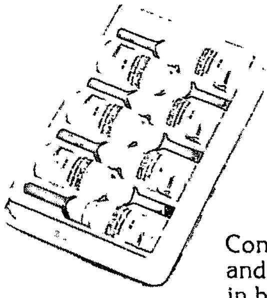

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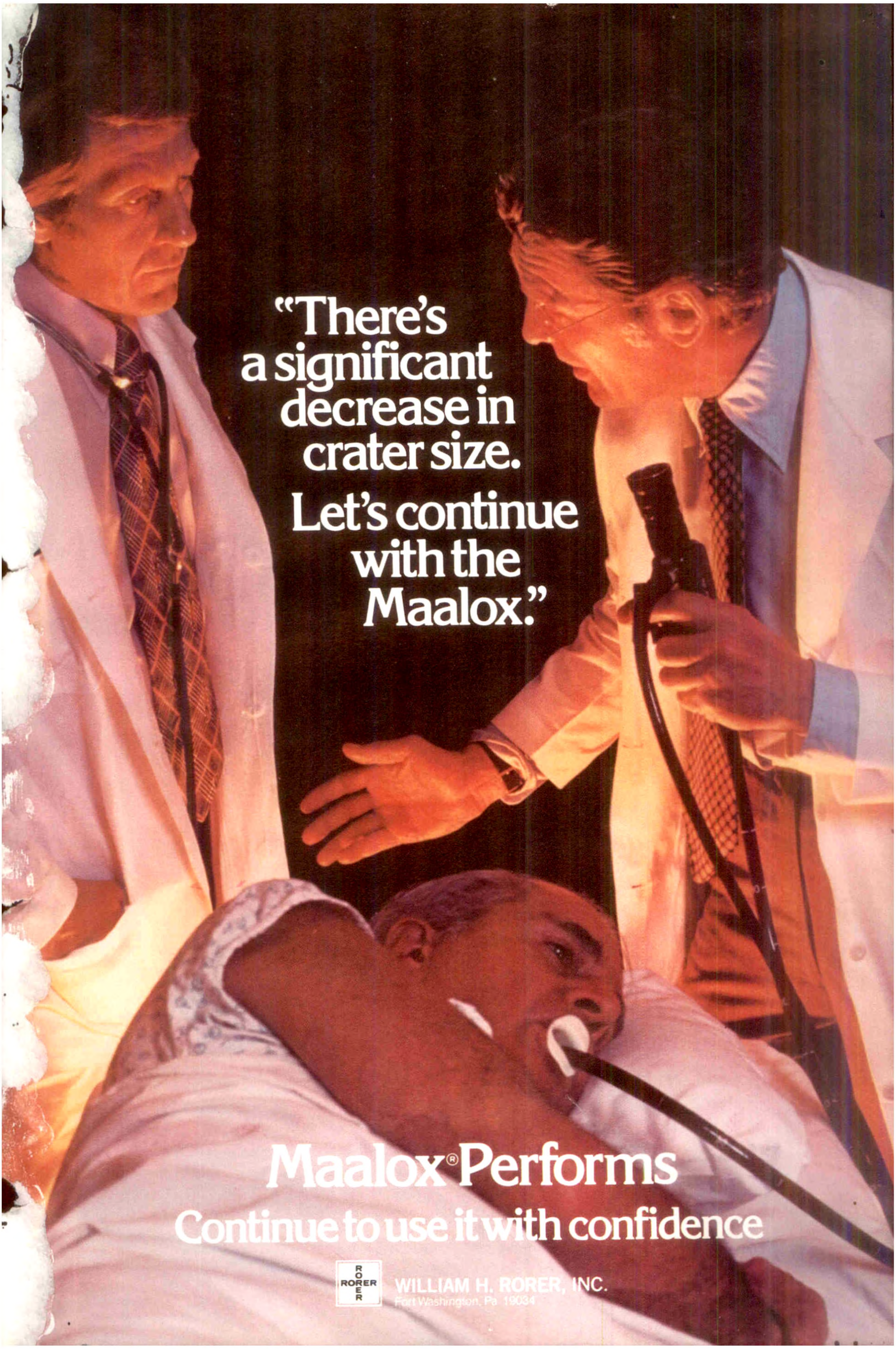
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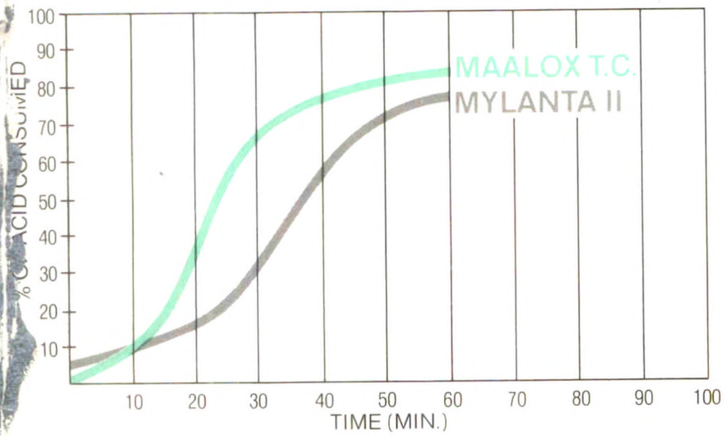

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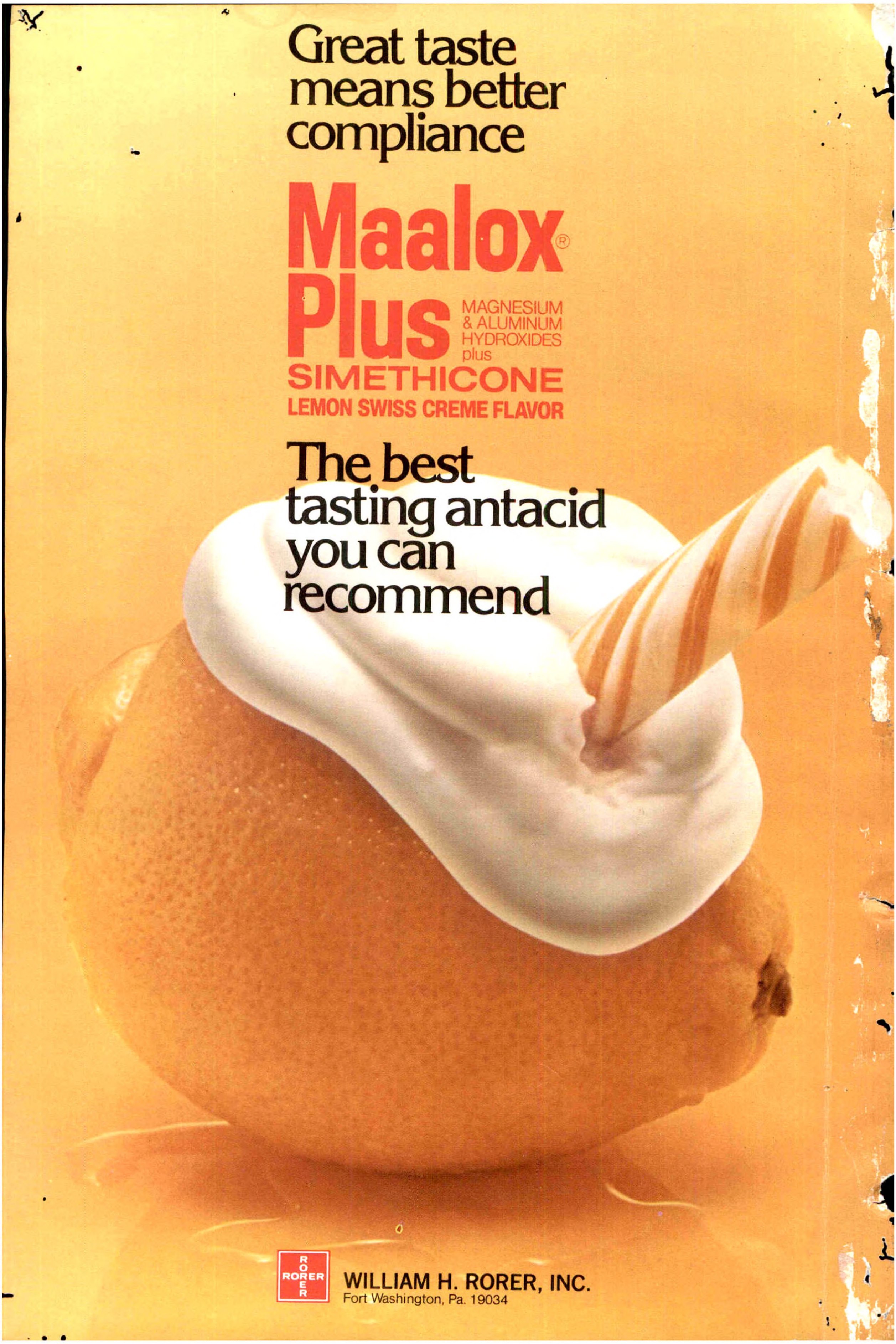
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